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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)

CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims and Abstract) – 81 pages
- ☐ Drawings – sheets
- ☒ Other (specify): Application data sheet

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Respectfully submitted,

Date: April 3, 2002

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CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to cyclic sulfamide derivatives, more specifically 1,1-dioxo-1,2,5-thiadiazolidine derivatives, pharmaceutical compositions containing them, and to methods of treating conditions associated with protein tyrosine phosphatase (PTPase) activity, in particular, PTPase-1B (PTP-1B) activity.

Description of Related Art

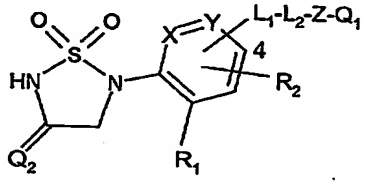
Type 2 (non-insulin-dependent) diabetes mellitus is often associated with an inability of insulin to function properly, referred to as insulin resistance. A current hypothesis for one of the causes of insulin resistance is faulty insulin signal transduction due to overactive PTPases, a large family of transmembrane or intracellular enzymes. The insulin signaling cascade begins with the binding of insulin to it's receptor, which initiates autophosphorylation of insulin receptor tyrosine residues, and terminates with the dephosphorylation of these tyrosine residues by insulin receptor associated PTPase. The enzymes that appear most likely to closely associate with the insulin receptor include intracellular PTP-1B (B. J. Goldstein, *J. Cellular Biochemistry* 1992, 48, 33; B. J. Goldstein, *Receptor* 1993, 3, 1-15; F. Ahmad and B. J. Goldstein, *Biochim. Biophys. Acta* 1995, 1248, 57-69). Inhibitors of insulin receptor associated PTPase may thus reduce insulin resistance by delaying deactivation of the insulin receptor and thereby prolonging insulin receptor signaling and increasing glucose clearance.

The insulin receptor requires autophosphorylation of specific tyrosine residues in the activation loop for activity. Upon binding insulin, the autophosphorylated receptor initiates a series of events resulting in glucose uptake from the blood. The insulin receptor is rapidly inactivated through dephosphorylation of these residues by associated protein tyrosine phosphatase, in particular PTP-1B. By inhibiting the dephosphorylation and prolonging the active state, inhibitors of the insulin receptor-associated PTPase may prolong insulin receptor signalling and enhance uptake of circulating glucose.

Inhibitors of PTP-1B have been demonstrated to improve insulin sensitivity in vivo, and PTP-1B inhibitors have also been shown to exhibit a beneficial reduction in triglycerides and lipids.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of the formula



(I)

wherein

R_1 is hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, nitro, trifluoromethyl, alkynyl, alkylthio, heteroaralkyl, heteroaralkoxy or heteroaryloxy; or

R_1 is optionally substituted alkyl, alkenyl, optionally substituted amino, aralkyl, aralkoxy, aralkylthio, aryloxy, arylthio or cycloalkyl provided that a substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative when Q_2 is oxygen; or

C-R_1 is nitrogen or N→O;

R_2 is hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, trifluoromethyl, nitro, optionally substituted amino, optionally substituted alkyl, alkylthio, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkylthio, aryloxy, heteroaryloxy, arylthio, or cycloalkyl; or

R_1 and R_2 combined together with the carbon atoms to which R_1 and R_2 are attached form an optionally substituted fused 5- to 6-membered aromatic or heteroaromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen, hydroxy, alkoxy, carboxy, optionally substituted alkyl, cycloalkyl, aryl or heteroaryl;

n is zero or an integer from 1 to 4;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl, sulfonyl, acyl or acylamino;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl

provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond located at the 4-position;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2; and

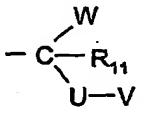
Q_2 is oxygen;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

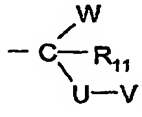
U is $-C(O)-$, $-S(O)_2-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

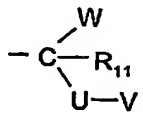
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

Q_2 is oxygen, sulfur or NR_{13} wherein

R_{13} is hydrogen, hydroxy or lower alkyl;

X and Y are independently CH or nitrogen; or

$-X=Y-$ is sulfur, oxygen or $-NR_{14}-$ wherein

R_{14} is hydrogen, optionally substituted alkyl, alkoxycarbonyl, acyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl or sulfonyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

In another aspect, the present invention provides pharmacological agents which are inhibitors of PTPases, in particular, the compounds of the present invention inhibit PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity. The compounds of the present invention may also be employed for inhibition of other enzymes with a phosphotyrosine binding region such as the SH2 domain. Accordingly, the compounds of formula I may be employed for prevention or treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance

is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to cyclic sulfamide derivatives, more specifically 1,1-dioxo-1,2,5-thiadiazolidine derivatives, pharmaceutical compositions containing them, methods for preparing the compounds and methods of treating conditions associated with PTPase activity, in particular PTP-1B activity. The compounds of the present invention may also be employed in combination with ligands for other enzymes with a phosphotyrosine binding region such as the SH2 domain.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or as part of a larger group.

The term "optionally substituted alkyl" refers to unsubstituted or substituted straight or branched chain hydrocarbon groups having 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: halo, hydroxy, cycloalkyl, alkanoyl, alkoxy, alkyloxyalkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, acylamino, carbamoyl, thiol, alkylthio, alkylthiono, sulfonyl, sulfonamido, sulfamoyl, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like.

The term "lower alkyl" refers to those alkyl groups as described above having 1 to 7, preferably 1 to 4 carbon atoms.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkenyl" refers to any of the above alkyl groups having at least 2 carbon atoms and further containing at least one carbon to carbon double bond. Groups having two to four carbon atoms are preferred.

The term "alkynyl" refers to any of the above alkyl groups having at least two carbon atoms and further containing at least one carbon to carbon triple bond. Groups having two to four carbon atoms are preferred.

The term "alkylene" refers to a straight chain bridge of 1 to 6 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$ wherein x is 1 to 6), which may be interrupted with one or more heteroatoms selected from oxygen, sulfur and nitrogen, and may be substituted with 1 to 3 substituents such as alkyl, alkoxy, halo, hydroxy, cycloalkyl, alkanoyl, alkyloxyalkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, acylamino, carbamoyl, thiol, alkylthio, alkylthiono, sulfonyl, sulfonamido, sulfamoyl, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like.

The term "cycloalkyl" refers to optionally substituted monocyclic, bicyclic or tricyclic hydrocarbon groups of 3 to 12 carbon atoms, each of which may be substituted by one or more substituents such as alkyl, halo, oxo, hydroxy, alkoxy, alkanoyl, acylamino, carbamoyl, alkylamino, dialkylamino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, sulfonyl, sulfonamido, sulfamoyl, heterocyclyl and the like.

Exemplary monocyclic hydrocarbon groups include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl and the like.

Exemplary bicyclic hydrocarbon groups include bornyl, indyl, hexahydroindyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl and the like.

Exemplary tricyclic hydrocarbon groups include adamantyl and the like.

The term "alkoxy" refers to alkyl-O-.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "alkanoyloxy" refers to alkyl-C(O)-O-.

The terms "alkylamino" and "dialkylamino" refer to alkyl-NH- and $(alkyl)_2N$-, respectively.

The term "alkanoylamino" refers to alkyl-C(O)-NH-.

The term "alkylthio" refers to alkyl-S-.

The term "alkylaminothiocarbonyl" refers to alkyl-NHC(S)-.

The term "trialkylsilyl" refers to $(alkyl)_3Si$-.

The term "trialkylsilyoxy" refers to $(alkyl)_3SiO$-.

The term "alkylthiono" refers to alkyl-S(O)-.

The term "alkylsulfonyl" refers to alkyl-$S(O)_2$-.

The term "alkoxycarbonyl" refers to alkyl-O-C(O)-.

The term "alkoxycarbonyloxy" refers to alkyl-O-C(O)O-.

The term "carbamoyl" refers to $H_2NC(O)$-, alkyl-NHC(O)-, $(alkyl)_2NC(O)$-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aralkyl-NHC(O)-, alkyl(aralkyl)-NC(O)- and the like.

The term "sulfamoyl" refers to $H_2NS(O)_2$-, alkyl-$NHS(O)_2$-, $(alkyl)_2NS(O)_2$-, aryl-$NHS(O)_2$-, alkyl(aryl)-$NS(O)_2$-, $(aryl)_2NS(O)_2$-, heteroaryl-$NHS(O)_2$-, aralkyl-$NHS(O)_2$-, heteroaralkyl-$NHS(O)_2$- and the like.

The term "sulfonamido" refers to alkyl-$S(O)_2$-NH-, aryl-$S(O)_2$-NH-, aralkyl-$S(O)_2$-NH-, heteroaryl-$S(O)_2$-NH-, heteroaralkyl-$S(O)_2$-NH-, alkyl-$S(O)_2$-N(alkyl)-, aryl-$S(O)_2$-N(alkyl)-, aralkyl-$S(O)_2$-N(alkyl)-, heteroaryl-$S(O)_2$-N(alkyl)-, heteroaralkyl-$S(O)_2$-N(alkyl)- and the like.

The term "sulfonyl" refers to alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aralkylsulfonyl, heteroaralkylsulfonyl and the like.

The term "optionally substituted amino" refers to a primary or secondary amino group which may optionally be substituted by a substituent such as acyl, sulfonyl, alkoxycarbonyl, cycloalkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, carbamoyl, alkylaminothiocarbonyl, arylaminothiocarbonyl and the like.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, biphenyl and diphenyl groups, each of which may optionally be substituted by one to four substituents such as alkyl, halo, hydroxy, alkoxy, acyl, alkanoyloxy, optionally substituted amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, carbamoyl, alkylthiono, sulfonyl, sulfonamido, heterocyclyl and the like.

The term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "aralkanoyl" refers to aralkyl-C(O)-.

The term "aralkylthio" refers to aralkyl-S-.

The term "aralkoxy" refers to an aryl group bonded directly through an alkoxy group.

The term "arylsulfonyl" refers to aryl-$S(O)_2$-.

The term "arylthio" refers to aryl-S-.

The term "aroyl" refers to aryl-C(O)-.

The term "aroylamino" refers to aryl-C(O)-NH-.

The term "aryloxycarbonyl" refers to aryl-O-C(O)-.

The term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4- to 7-membered monocyclic, 7- to 12-membered bicyclic, or 10- to 15-membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or a carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, 1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl and the like.

Exemplary bicyclic heterocyclic groups include indolyl, dihydroidolyl, benzothiazolyl, benzoxazinyl, benzoxazolyl, benzothienyl, benzothiazinyl, quinuclidinyl, quinolinyl, tetrahydroquinolinyl, decahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, decahydroisoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]-pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, 1,3-dioxo-1,3-dihydroisoindol-2-yl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), phthalazinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, dibenzoazepinyl, dithienoazepinyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, phenoxazinyl, phenothiazinyl, xanthenyl, carbolinyl and the like.

The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;
(d) oxo (i.e. = O);
(e) optionally substituted amino, alkylamino or dialkylamino;
(f) alkoxy;
(g) cycloalkyl;
(h) carboxy;
(i) heterocyclooxy;
(j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;
(k) mercapto;
(l) nitro;
(m) cyano;
(n) sulfamoyl or sulfonamido;
(o) aryl;
(p) alkylcarbonyloxy;
(q) arylcarbonyloxy;
(r) arylthio;
(s) aryloxy;
(t) alkylthio;
(u) formyl;
(v) carbamoyl;
(w) aralkyl; or
(x) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, acylamino, alkylamino, dialkylamino or halo.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

The term "heteroaryl" refers to an aromatic heterocycle, for example monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl, and the like, optionally substituted by e.g. lower alkyl, lower alkoxy or halo.

The term "heteroarylsulfonyl" refers to heteroaryl-$S(O)_2$-.

The term "heteroaroyl" refers to heteroaryl-C(O)-.

The term "heteroaroylamino" refers to heteroaryl-C(O)NH-

The term "heteroaralkyl" refers to a heteroaryl group bonded through an alkyl group.

The term "heteroaralkanoyl" refers to heteroaralkyl-C(O)-.

The term "heteroaralkanoylamino" refers to heteroaralkyl-C(O)NH-.

The term "acyl" refers to alkanoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl and the like.

The term "acylamino" refers to alkanoylamino, aroylamino, heteroaroylamino, aralkanoylamino, heteroaralkanoylamino and the like.

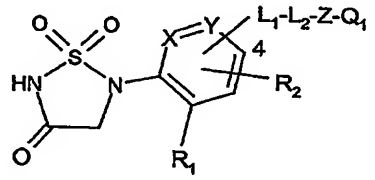
Preferred are the compounds of formula I wherein

Q_2 is oxygen;

X and Y are CH; or

-X=Y- is sulfur; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Further preferred are the compounds of the formula



(IA)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, alkylthio, heteroaralkyl or heteroaralkoxy; or

R_1 is optionally substituted alkyl, aralkyl, aralkoxy or aryloxy provided that a substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative;

R_2 is hydrogen; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen or optionally substituted alkyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond located at the 4-position;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero; and

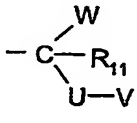
Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

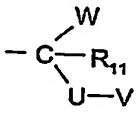
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

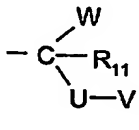
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

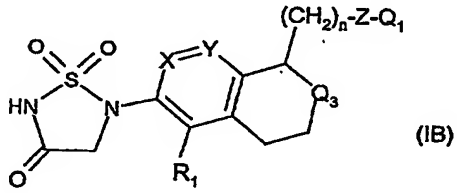
V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA of the formula



(IB)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or

acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

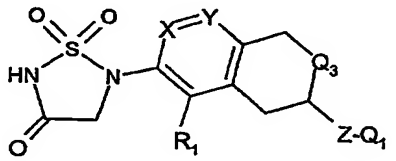
q is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA of the formula



(IC)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl,

cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula IA wherein

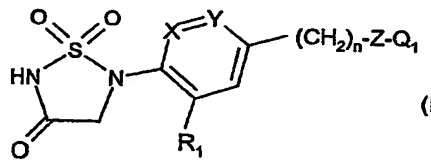
R_2 is hydrogen;

L_1 is a single bond;

L_2 is $-(CH_2)_n-$ wherein n is zero or an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Further preferred are the compounds of formula IA of the formula



(ID)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl or alkylthio; or

R_1 is optionally substituted alkyl, aralkyl, aralkoxy or aryloxy provided that a substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or

acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl

provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 is hydrogen;

X and Y are CH;

L_2 is $-(CH_2)_n-$ wherein n is zero; and

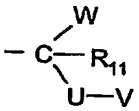
Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

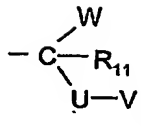
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

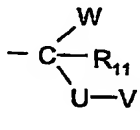
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

-X=Y- is sulfur;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

R_1 is bromide;

X and Y are CH;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mO(CH_2)_r-$ or $-(CH_2)_mS(CH_2)_r-$ wherein

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mNR_9(CH_2)_r-$ wherein

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

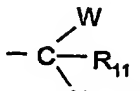
q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is -C(O)- or $-(CH_2)_r-$ in which r is zero;

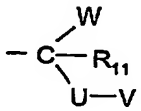
V is aryl, heteroaryl, optionally substituted alkyl or cycloalkyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

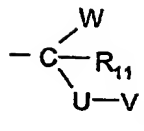
V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Preferred are the compounds of formula ID wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl or alkoxy; or R_{12} is $-NR_4R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Particular embodiments of the invention are:

1,1-Dioxo-5-phenyl-1,2,5-thiadiazolidin-3-one;

5-(2,4-Diamino-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid methyl ester;

3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid;

5-(4-Aminomethyl-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester;

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid;

5-(4-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid benzyl ester;

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid;

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide;

(S)-2-Acetylamino-3-phenyl-N-{(S)-1-(4-phenyl-butylcarbamoyl)-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-propionamide;

[4-(2-{(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionylamino}-ethyl)-phenyl]-acetic acid;

2-[4-(2-Benzoylamino-2-{1-carbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethylcarbamoyl}-ethyl)-phenoxy]-malonic acid;

(S)-2-(Biphenyl-4-sulfonylamino)-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-(Biphenyl-4-sulfonylamino)-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-(3,3-diphenyl-propyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide;

(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide;

(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide; and

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

Pharmaceutically acceptable salts of any acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethylammonium, diethylammonium, and tris(hydroxymethyl)methyl-ammonium salts and salts with amino acids.

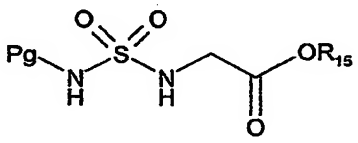
Similarly acid addition salts, such as of mineral acids, organic carboxylic, and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are possible provided a basic group, such as pyridyl, constitutes part of the structure.

Prodrug derivatives of any compound of the invention are derivatives of said compounds which following administration release the parent compound in vivo via some chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound. Exemplary prodrug derivatives are, e.g., esters of free carboxylic acids and S-acyl and O-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, e.g., lower alkyl esters, cycloalkyl esters, lower

alkenyl esters, benzyl esters, mono or disubstituted lower alkyl esters such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester, and the like conventionally used in the art.

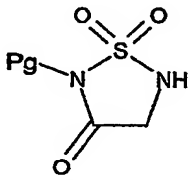
The compounds of the invention depending on the nature of the substituents, may possess one or more asymmetric centers. The resulting diastereoisomers, enantiomers and geometric isomers are encompassed by the instant invention.

Compounds of formula I may be prepared by cyclizing compounds of the formula



(II)

wherein Pg is an appropriate N-protecting group such as 4-methoxybenzyl, 2,4-dimethoxybenzyl or 2-trimethylsilylethyl and R_{15} is hydrogen to afford compounds of the formula



(III)

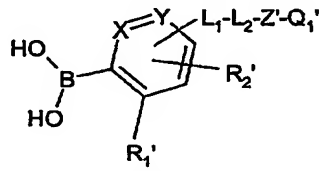
wherein Pg has a meaning as defined herein above, by treatment with a coupling agent such as diisopropyl carbodiimide (DIC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) in the presence a base such as triethylamine (TEA) or N-methyl-morpholine (NMM) in an organic solvent such as tetrahydrofuran (THF), N,N-dimethyl-formamide (DMF) or dichoromethane (CH_2Cl_2). The reaction may be carried out in the presence of an additive such as of hydroxybenzotriazole (HOBt).

Compounds of formula II wherein R_{15} is an alkyl group such as methyl, ethyl or t-butyl and the like may be obtained analogously to a literature procedure described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta.* **1999**, *82*, 2432-47.

Compounds of formula II wherein R_{15} is an alkyl group as defined herein above may be converted to compounds of formula II wherein R_{15} is hydrogen according to methods well known in the art, e.g. compounds of formula II in which R_{15} is methyl or ethyl can be treated

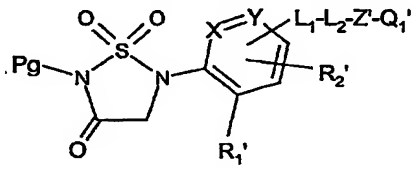
with aqueous base such as sodium or potassium hydroxide in an organic solvent such as THF, 1,4-dioxane, methanol (MeOH) or ethanol (EtOH) to afford compounds of formula II wherein R_{15} is hydrogen, or compounds of formula II in which R_{15} is t-butyl may be treated with an acid such as hydrochloric acid (HCl) or trifluoroacetic acid (TFA) in an organic solvent such as CH_2Cl_2 or ethyl acetate (EtOAc) to afford compounds of formula II wherein R_{15} is hydrogen.

Compounds of formula III wherein Pg has a meaning as defined herein can be coupled with a variety of boronic acids of the formula



(IV)

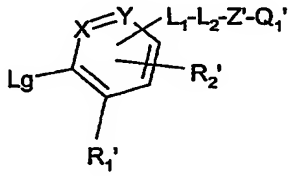
wherein L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, in the presence of a copper catalyst such as copper(II) acetate and a base such as cesium(II) carbonate (Ce_2CO_3) or TEA in an organic solvent such as THF, 1,4-dioxane or CH_2Cl_2 to form compounds of the formula



(V)

wherein Pg, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively.

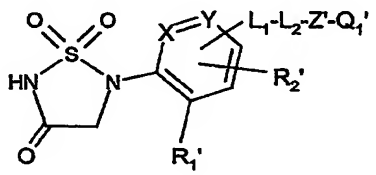
Alternatively, compounds of formula V wherein Pg, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, may be obtained by reacting a compound of formula III wherein Pg has a meaning as defined herein with compounds of the formula



(VI)

wherein Lg represents a leaving group such as halide or trifluoromethanesulfonate, preferably fluoride or chloride, and L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, using conditions well know in the art or using methods described herein or modifications thereof, e.g., a compound of formula III may be first treated with a base such as Ce_2CO_3, or sodium, lithium or potassium bis(trimethylsilyl) amide in an inert organic solvent such as THF or 1,4-dioxane followed by reaction with a compound of formula VI at a temperature ranging from room temperature (RT) to 110°C.

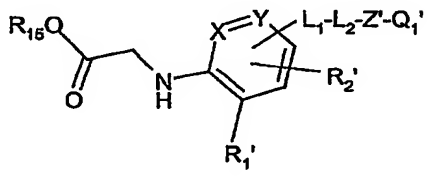
Compounds of formula V wherein Pg, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, can be converted to compounds of the formula



(I')

by removal of the N-protecting group according to methods well known in the art, e.g. in particular when Pg is 4-methoxybenzyl or 2,4-dimethoxybenzyl group using hydrogen in the presence of a catalyst such as palladium on carbon in a polar organic solvent such as MeOH or EtOAc, or by treatment with an acid such as TFA in an organic solvent such as CH_2Cl_2, preferably in the presence of an additive such as t-butyldimethylsilane or triethylsilane, or in particular when Pg is trimethylsilylethyl group using a fluoride reagent such as tetra-n-butylammoniumfluoride in an organic solvent such as THF or 1,4-dioxane.

In addition, compounds of formula I' wherein L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, may be prepared by condensing compounds of the formula

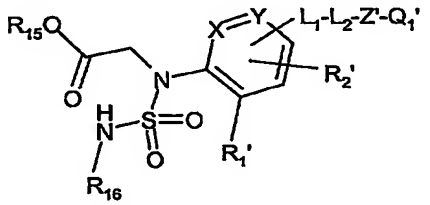


(VII)

wherein R_{15} has a meaning as defined herein above, with sulfamoyl chloride analogs of the formula

$$ClS(O)_2NHR_{16} \qquad \text{(VIII)}$$

wherein R_{16} is hydrogen or alkoxycarbonyl such as t-butoxycarbonyl or 2-trimethylsilyl-ethoxycarbonyl in the presence of a base such as TEA or NMM in an organic solvent such as acetonitrile (MeCN), CH_2Cl_2 or THF to form compounds of the formula



(IX)

wherein R_{15}, R_{16}, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively. Compounds of formula VIII wherein R_{16} is alkoxycarbonyl may be obtained by reacting chlorosulfonyl isocyanate with the appropriate alcohol in an organic solvent such as MeCN, CH_2Cl_2 or THF. Compounds of formula VII may be prepared using methods well known in the art or according to methods described herein or modifications thereof, e.g., according to the method described by Tohru Fukuyama et. al., *Tet. Lett.* **1997**, *38* (33), 5831-34.

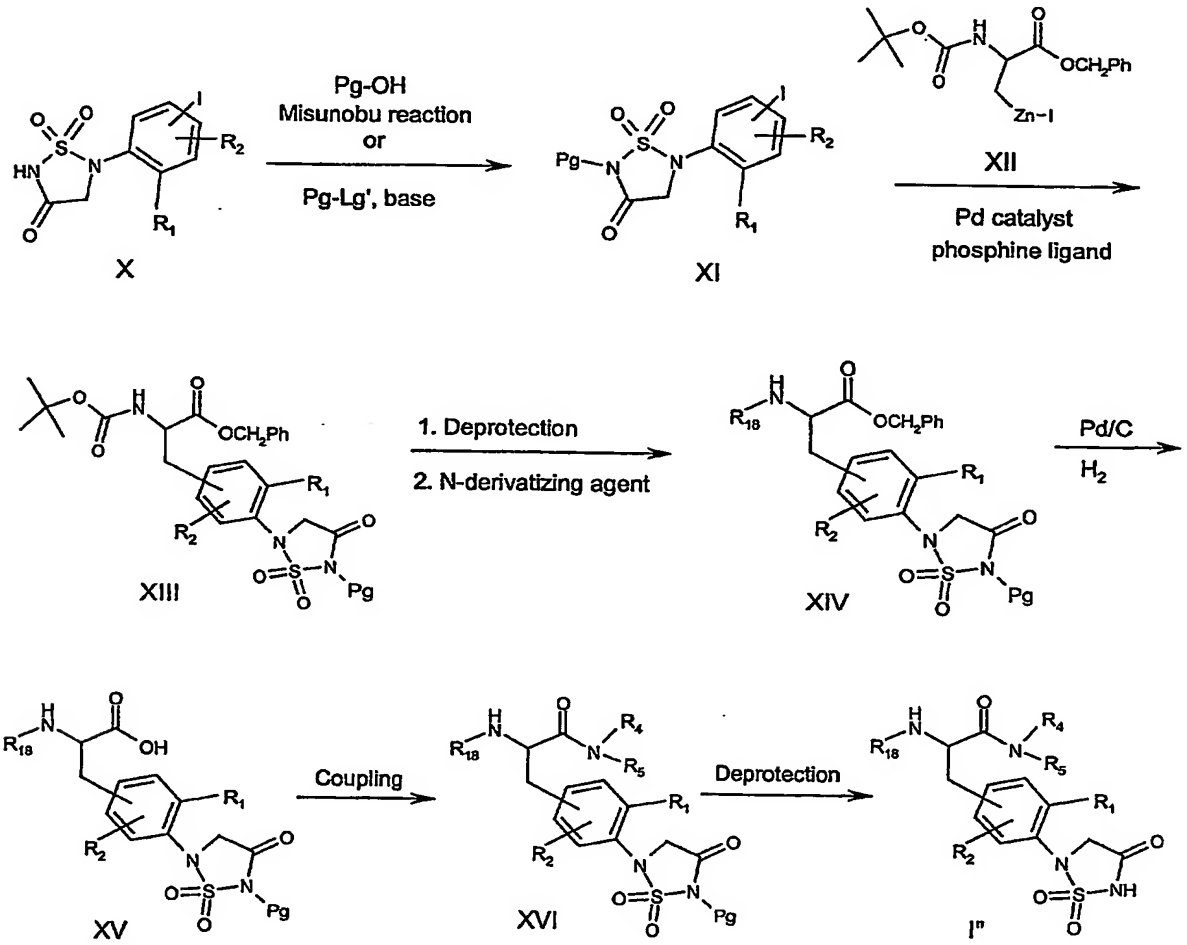
Compounds of formula IX wherein R_{15}, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, and R_{16} is alkoxycarbonyl may be converted to compounds of formula IX wherein R_{16} is hydrogen according to methods known in the art or using methods described herein or modifications thereof, e.g., compounds of formula IX wherein R_{16} is t-butoxycarbonyl may be treated with an acid such as TFA, neat or in an organic solvent such as CH_2Cl_2, or compounds of formula IX wherein R_{16} is 2-trimethylsilylethoxycarbonyl may be treated with a fluoride reagent such as tetra-n-butylammoniumfluoride in an organic solvent such as THF or 1,4-dioxane to afford compounds of formula IX wherein R_{16} is hydrogen.

Compounds of formula IX wherein R_{15}, L_1, L_2, X and Y have meanings as defined herein, and R_1', R_2', Z' and Q_1' represent R_1, R_2, Z and Q_1 as defined herein or R_1', R_2', Z' and Q_1' are groups convertible to R_1, R_2, Z and Q_1, respectively, and R_{16} is hydrogen can be

cyclized to form compounds of formula I' using methods and conditions well known in the art or as illustrated with Examples herein or modifications thereof.

In a particular embodiment of the invention, compounds of formula I may be prepared as illustrated in Scheme I.

Scheme I

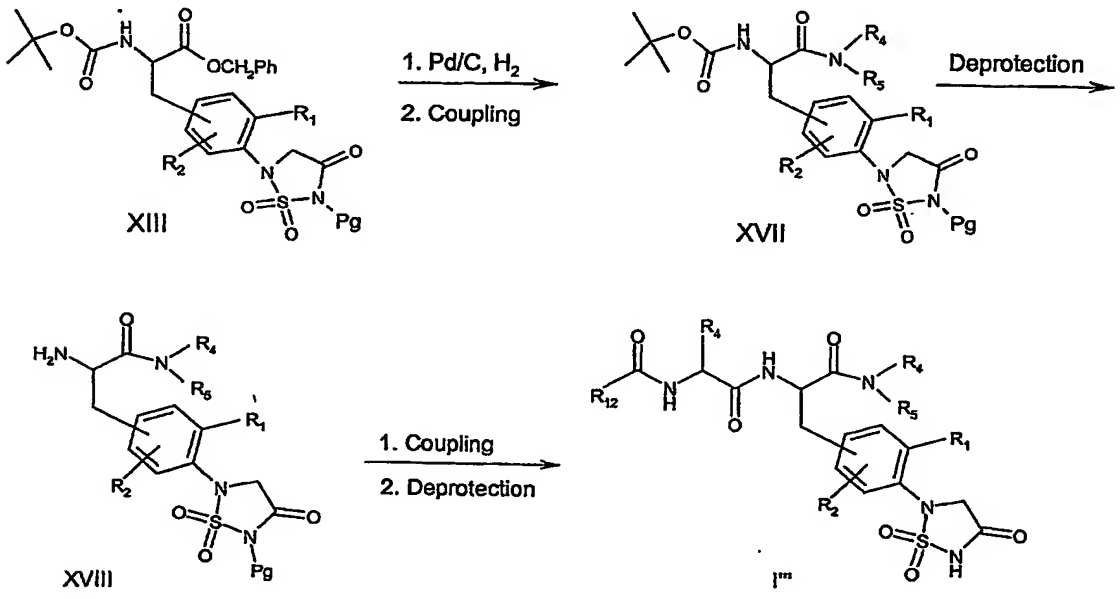


Compounds of formula X wherein R_1 and R_2 have meanings as defined herein, may be reacted with alcohols of the formula PgOH wherein Pg is a N-protecting group as defined herein under Mitsunobu conditions, e.g., in the presence of triphenylphoshine and diethyl azodicarboxylate in an organic solvent such as THF, to afford compounds of formula XI. Alternatively, compounds of formula X may be converted to compounds of formula XI by treatment with an alkylating agent of the formula Pg-Lg' in which Pg has meanings as defined herein and Lg' represents a leaving group, such as bromide, chloride, methane-

sulfonate or trifluoromethanesulfonate, in the presence of a base such as 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) in an inert solvent such as CH_2Cl_2, THF or DMF. The subsequent reaction between compounds of formula XI and the organozinc reagent XII may be carried out in the presence of palladium(0) catalyst such as tris(dibenzylideneacetone)-dipalladium(0) acetate and a phosphine ligand such as tritolylphosphine in an organic solvent such as DMF to form compounds of formula XIII. Compounds of formula XIII may be treated with an acid such as TFA to remove the t-butoxycarbonyl protecting group. The resulting amines or acid addition salts thereof are then reacted with a N-derivatizing agent, such as an activated derivative of a carboxylic acid, a chloroformate, an isocyanate or a sulfonyl chloride in the presence of a base such as TEA, diisopropylethylamine or NMM in an inert solvent such as MeCN, CH_2Cl_2, DMF or THF to obtain compounds of formula XIV wherein R_{18} is $-C(O)R_5$, $-C(O)OR_5$, $-C(O)NR_4R_5$ or $-S(O)_2R_5$, respectively, and R_4 and R_5 have meanings as defined herein. The benzyl ester may be removed by catalytic hydrogenation to afford carboxylic acids of formula XV. Coupling of an activated derivative of a carboxylic acid of formula XV with amines of formula HNR_4R_5 yields amides of formula XVI wherein R_4 and R_5 have meanings as defined herein. Finally, treatment with an acid such as TFA affords compounds of formula I".

In another embodiment of the invention, compounds of formula I may be prepared as illustrated in Scheme II.

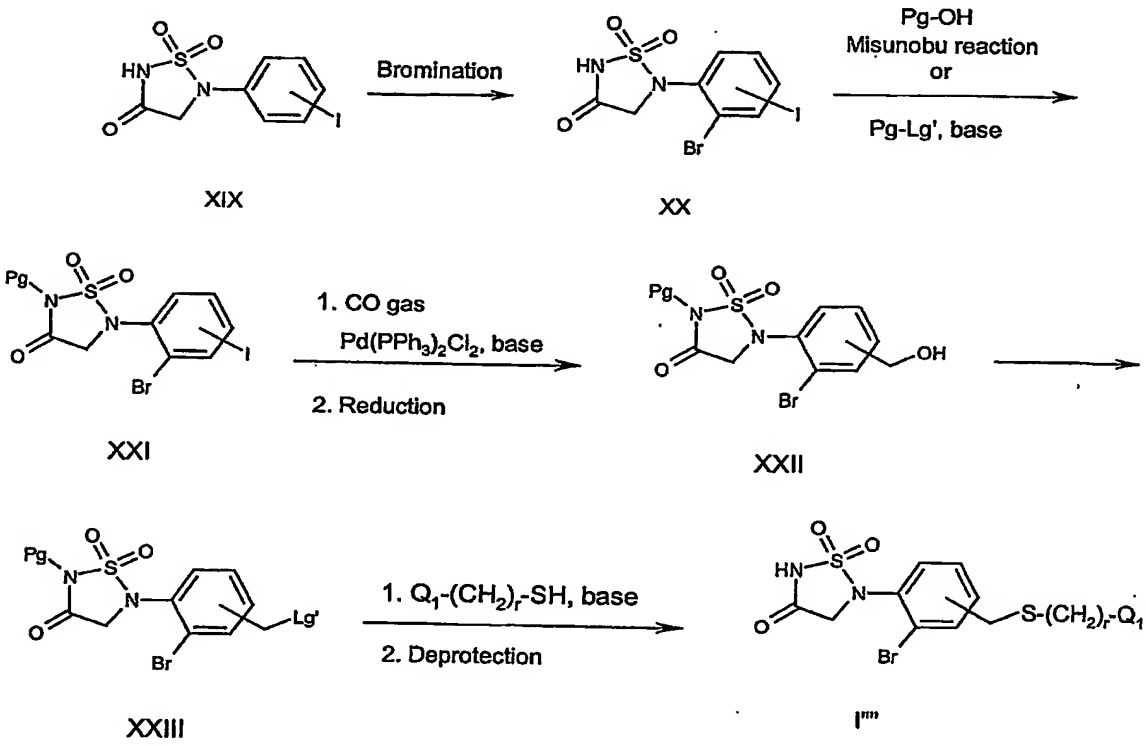
Scheme II



In the processes cited herein, activated derivatives of carboxylic acids, e.g., those of formula XV, include acid chlorides, bromides and fluorides, mixed anhydrides, lower alkyl esters, and activated esters thereof, and adducts formed with coupling agents such as EDCI, DIC, O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N',N'-tetramethyluronium tetrafluoroborate and the like. Mixed anhydrides are preferably such from pivalic acid, or lower alkyl hemiesters of carbonic acids, such as ethyl or isobutyl analogs. Activated esters include, for example, succinimido, phthalimido or 4-nitrophenyl esters. The reaction of an activated derivative of a carboxylic acid, e.g., those of formula XV, with an amine may be carried out in the presence of a base such as TEA, diisopropylethylamine or NMM in an inert solvent such as CH_2Cl_2, DMF or THF. Carboxylic acids of formula XV can be converted to their activated derivatives using methods described herein or modifications thereof or using methods well known in the art.

In yet another embodiment of the invention, compounds of formula I may be prepared as illustrated in Scheme III.

Scheme III



Compounds of formula XIX may be converted to compounds of formula XX by the treatment with a brominating agent such as dibromo isocyanuric acid in an organic solvent

such as THF or 1,4-dioxane. Compounds of formula XX may then be reacted with alcohols of the formula PgOH wherein Pg is a N-protecting group as defined herein under Mitsunobu conditions, e.g., in the presence of triphenylphoshine and diethyl azodicarboxylate in an organic solvent such as THF, to afford compounds of formula XXI. Alternatively, compounds of formula XX may be converted to compounds of formula XXI by treatment with an alkylating agent of the formula Pg-Lg' in which Pg has meanings as defined herein and Lg' represents a leaving group, such as bromide, chloride, methanesulfonate or trifluoromethanesulfonate, in the presence of a base such as DBU in an inert solvent such as CH_2Cl_2, THF or DMF. The subsequent reaction with carbon monoxide gas (CO) in the presence of a palladium catalyst such as bis(triphenylphoshine)palladium(II) chloride and a base such as sodium bicarbonate in an organic solvent such as DMF, followed by treatment with a reducing agent such as sodium borohydride, or sodium cyanoborohydride in an inert solvent such as THF affords alcohols of formula XXII. Compounds of formula XXII may be converted to compounds of formula XXIII wherein Lg' represents a leaving group as defined herein above using methods well known in the art. Compounds of formula XXIII may be reacted with thiols of the formula Q_1-$(CH_2)_r$-SH wherein r is zero or 1, and Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl, in the presence of base such as Ce_2CO_3 in an organic solvent such as DMF. The resulting sulfides may then be deprotected by treatment with acid such as TFA to afford compounds of formula I''''.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl, and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl, and hydroxyl groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxyl groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxyl group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973, T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1991.

The above mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures (preferably at or near the boiling point of the solvents used), and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

Compounds of the invention and intermediates can also be converted into each other according to methods generally known per se.

The invention also relates to any novel starting materials, intermediates and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (cis or trans) isomers, optical isomers (antipodes), racemates, or mixtures thereof. The aforesaid possible isomers or mixtures thereof are within the purview of this invention.

Any resulting mixtures of isomers can be separated on the basis of the physico-chemical differences of the constituents, into the pure geometric or optical isomers, diastereoisomers, racemates, for example by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g. by separation of the diastereoisomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. The carboxylic acid intermediates can thus be resolved into their optical antipodes e.g. by fractional crystallization of d- or l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, quinidine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts. Racemic products can also be resolved by chiral chromatography, e.g. high pressure liquid chromatography using a chiral adsorbent.

Finally, compounds of the invention are either obtained in the free form, as a salt thereof if salt forming groups are present or as prodrug derivatives thereof.

Compounds of the instant invention which contain acidic groups, in particular the NH group of the 1,1-dioxo-1,2,5-thiadiazolidin-3-one moiety, may be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts like sodium. lithium and potassium salts, alkaline earth metal salts like calcium and magnesium salts, ammonium salts with organic bases, e.g., trimethylamine salts, diethylamine salts, tris(hydroxymethyl)methylamine salts, dicyclohexylamine salts and N-methyl-D-glucamine salts, salts with amino acids like arginine, lysine, and the like. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g. diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

Compounds of the invention having basic groups can be converted into acid addition salts, especially pharmaceutically acceptable salts. These are formed, for example, with inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric or hydrohalic acid, or with organic carboxylic acids, such as (C_1-C_4)-alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, for example glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or with organic sulfonic acids, such as (C_1-C_4)-alkylsulfonic acids (for example methanesulfonic acid) or arylsulfonic acids which are unsubstituted or substituted (for example by halogen). Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

In view of the close relationship between the free compounds, the prodrug derivatives and the compounds in the form of their salts, whenever a compound is referred to in this context, a prodrug derivative and a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, to inhibit protein tyrosine phosphatases, and for the treatment of conditions associated with PTPase activity, in particular, PTP-1B activity. Such conditions include insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system. The said pharmaceutical compositions comprise a therapeutically effective amount of a pharmacologically active compound of the instant invention, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising a therapeutically effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbants, colorants, flavors and

sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to75%, preferably about 1 to 50%, of the active ingredient.

Suitable formulations for transdermal application include a therapeutically effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The pharmaceutical formulations contain a therapeutically effective amount of a compound of the invention as defined above, either alone or in a combination with another therapeutic agent, e.g., each at an effective therapeutic dose as reported in the art. Such therapeutic agents include insulin, insulin derivatives and mimetics, insulin secretagogues such as the sulfonylureas, e.g., Glipizide and Amaryl, insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide, PPARα and/or PPARγ ligands, biguanides such as metformin, aldose reductase inhibitors, alpha-glucosidase inhibitors such as acarbose, glycogen phosphorylase inhibitors, GLP-1, GLP-1 analogs such as Exendin-4 and GLP-1 mimetics, and DPP-IV inhibitors. Thus, the methods of treatment or prevention described herein may further include administering to mammals a second anti-diabetic compound in an amount effective to treat or prevent diabetes. Similarly, the methods of treatment of diabetes may include the administration of a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor such as lovastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, fluidostatin and rivastatin, a squalene synthase inhibitor or FXR and LXR ligands, cholestyramine, fibrates, nicotinic acid, and aspirin in an amount effective to improve the lipid profile. The combination of a cholesterol lowering agent, anti-hypertensive agent or anti-obesity agent with a PTPase inhibitor, in particular a

PTP-1B inhibitor, may be beneficial in the treatment or prevention of atherosclerosis, hypertension, obesity and other conditions that often are associated with Type 2 diabetes. A compound of the present invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

A unit dosage for a mammal of about 50 to 70 kg may contain between about 1 mg and 1000 mg, advantageously between about 5 mg to 500 mg of the active ingredient. The therapeutically effective dosage of a compound of formula I is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, on the form of administration, and on the compound involved.

The compounds of the present invention are inhibitors of PTPases, in particular PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity, in particular with PTP-1B activity, as described herein, e.g. insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels, and conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is a component. In addition, the compounds of this invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.

The above-cited properties are demonstrable in vitro and in vivo tests, using advantageously mammals, e.g. mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. preferably aqueous solutions, and in vivo either enterally, parenterally, advantageously intravenously, e.g. as a suspension or in aqueous solution. The dosage in vitro may range between about 10^{-3} molar and 10^{-9} molar concentrations. A therapeutically effective amount in vivo may range depending on the route of administration, between about 1 and 500 mg/kg, preferably between about 5 and 100 mg/kg.

The activity of a compound according to the invention can be assessed by the following methods or methods well described in the art:

The PTP-1B inhibitory activity in vitro may be determined as follows:

Assessment of human PTP-1B (hPTP-1B) activity in the presence of various agents is determined by measuring the amount of inorganic phosphate released from a phosphopeptide substrate using a 96-well microtiter plate format. The assay (100 µL) is performed in an assay buffer comprised of 50 mM TRIS (pH 7.5), 50 mM NaCl, 3 mM DTT at ambient temperature. The assay is typically performed in the presence of 0.4% dimethyl sulfoxide (DMSO). However, concentrations as high as 10% are used with certain poorly soluble compounds. A typical reaction is initiated by the addition of 0.4 pmoles of hPTP-1B (amino acids 1-411) to wells containing assay buffer, 3 nmoles of the synthetic phosphopeptide substrate (GNGDpYMPMSPKS), and the test compound. After 10 min, 180 µL malachite green reagent (0.88 mM malachite green, 8.2 mM ammonium molybdate, aqueous 1 N HCl, and 0.01% Triton X-100) is added to terminate the reaction. Inorganic phosphate, a product of the enzyme reaction, is quantitiated after 15 min as the green color resulting from complexing with the Malichite reagent and is determined as an A_{620} using a Molecular Devices (Sunnyvale, CA) SpectraMAX Plus spectrophotometer. Test compounds are solubilized in 100 % DMSO (Sigma, D-8779) and diluted in DMSO. Activity is defined as the net change in absorbance resulting from the activity of the uninhibited $hPTP\text{-}1B_{[1\text{-}411]}$ minus that of a tube with acid-inactivated $hPTP\text{-}1B_{[1\text{-}411]}$.

The $hPTP\text{-}1B_{[1\text{-}411]}$ is cloned by PCR from a human hippocampal cDNA library (Clonetech) and inserted into a pET 19-b vector (Novagen) at the Nco1 restriction site. E. coli strain BL21 (DE3) is transformed with this clone and stored as a stock culture in 20% glycerol at –80° C. For enzyme production, a stock culture is inoculated into Lb/Amp and grown at 37°C. Expression of PTP-1B is initiated by induction with 1mM IPTG after the culture had reached an OD_{600} = 0.6. After 4h, the bacterial pellet is collected by centrifugation. Cells are resuspended in 70mL lysis buffer (50mM Tris, 100 mM NaCl, 5mM DTT, 0.1% Triton X-100, pH7.6), incubated on ice for 30 min then sonicated (4 X 10sec bursts at full power). The lysate is centrifuged at 100,000 x g for 60 min and the supernatant is buffer exchanged and purified on a cation exchange POROS 20SP column followed by an anion exchange Source 30Q (Pharmacia) column, using linear NaCl gradient elutions. Enzyme is pooled, adjusted to 1mg/mL and frozen at –80° C.

Competitive binding to the active site of the enzyme can be determined as follows:

Ligand binding is detected by acquiring $^{1}H\text{-}^{15}N$ HSQC spectra on 250 µL of 0.15 mM $PTP\text{-}1B_{[1\text{-}298]}$ in the presence and absence of added compound (1-2 mM). The binding is determined by the observation of ^{15}N- or ^{1}H-amide chemical shift changes in two

dimensional HSQC spectra upon the addition of a compound to ^{15}N-label protein. Because of the ^{15}N spectral editing, no signal from the ligand is observed, only protein signals. Thus, binding can be detected at high compound concentrations. Compounds which caused a pattern of chemical shift changes similar to the changes seen with known active site binders are considered positive.

All proteins are expressed in E. coli BL21 (DE3) containing plasmids constructed using pET19b vectors (Novagen). Uniformly ^{15}N-labeled PTP-$1B_{1-298}$ is produced by growth of bacteria on minimal media containing ^{15}N-labeled ammonium chloride. All purification steps are performed at 4°C. Cells (~15 g) are thawed briefly at 37°C and resuspended in 50 mL of lysis buffer containing 50 mM Tris-HCl, 150 mM NaCl, 5 mM DTT, pH 8.0 containing one tablet of Complete (EDTA-free) protease cocktail (Boehringer Mannheim), 100 µM PMSF and 100 µg/mL DNase I. The cells are lysed by sonication. The pellet is collected at 35,000 x g, resuspended in 25 mL of lysis buffer using a Polytron and collected as before. The two supernatants are combined and centrifuged for 30 min at 100,000 x g. Diafiltration using a 10 kD MWCO membrane is used to buffer exchange the protein and reduce the NaCl concentration prior to cation exchange chromatography. Diafiltration buffer contained 50 mM MES, 75 mM NaCl, 5 mM DTT, pH 6.5. Soluble supernatant is then loaded onto a POROS 20 SP (1 x 10 cm) column equilibrated with cation exchange buffer (50 mM MES and 75 mM NaCl, pH 6.5) at a rate of 20 mL/min. Protein is eluted from the column using a linear salt gradient (75-500 mM NaCl in 25 CV). Fractions containing PTP-1B's are identified and pooled according to SDS-PAGE analyses. PTP-$1B_{1-298}$ is further purified by anion exchange chromatography using a POROS 20 HQ column (1 x 10 cm). The pool from cation exchange chromatography is concentrated and buffer exchanged in 50 mM Tris-HCl, pH 7.5 containing 75 mM NaCl and 5 mM DTT. Protein is loaded onto column at 20 mL/min and eluted using a linear NaCl gradient (75-500 mM in 25 CV). Final purification is performed using Sephacryl S-100 HR (Pharmacia)(50 mM HEPES, 100 mM NaCl, 3 mM DTT, pH 7.5). The NMR samples are composed of uniformly ^{15}N-labeled PTP-$1B_{1-298}$ (0.15 mM) and inhibitor (1-2 mM) in a 10%D_2O/90%H_2O Bis-Tris-d_{19} buffer (50 mM, pH = 6.5) solution containing NaCl (50 mM), DL-1, 4-Dithiothreitol-d_{10} (5mM) and Sodium azide (0.02%).

The ^1H-^{15}N HSQC NMR spectra are recorded at 20°C, on Bruker DRX500 or DMX600 NMR spectrometers. In all NMR experiments, pulsed field gradients are applied to afford the suppression of solvent signal. Quadrature detection in the indirectly detected dimensions is accomplished by using the States-TPPI method. The data are processed

using Bruker software and analyzed using NMRCompass software (MSI) on Silicon Graphics computers.

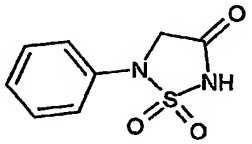
The glucose and insulin lowering activity in vivo may be evaluated as follows:

Adult male C57BL ob/ob mice (Jackson Lab, Bar Harbor, ME) at the age of 11 weeks are housed six per cage in a reversed light cycle room (light on from 6:00 p.m. to 6:00 a.m.) and given access to Purina rodent chow and water *ad libitum*. On day 1 tail blood samples are taken at 8:00 am and plasma glucose levels are determined. The animals are randomly assigned to the control and compound groups. The means of plasma glucose values of the groups are matched. Animals are then orally dosed with vehicle (0.5% carboxymethyl-cellulose with 0.2% Tween-80) or compounds (at 30 mg/kg) in vehicle. The mice are dosed daily for a total of 3 days. On day 4 basal blood samples are taken. The plasma samples are analyzed for glucose concentrations using a YSI2700 Dual Channel Biochemistry Analyzer (Yellow Springs Instrument Co., Yellow Springs, OH) and insulin concentrations using an ELISA assay.

The following Examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mmHg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis, melting point (mp) and spectroscopic characteristics (e.g. MS, IR, NMR). Abbreviations used are those conventional in the art. The concentration for $[\alpha]_D$ determinations is expressed in mg/mL.

Example 1

1,1-Dioxo-5-phenyl-1,2,5-thiadiazolidin-3-one sodium salt



A. N-sulfamoylated-N-phenylglycine ethyl ester

A solution N-phenylglycine ethyl ester (1.0 g, 5.58 mmol) and TEA (1.69 g, 16.7 mmol) in MeCN, 3mL is added dropwise to a freshly prepared solution of sulfamoyl chloride (5.58 mmol) in MeCN (5mL) over 20 min. The mixture is stirred at room temperature (RT) for 16 h. The solvent is evaporated and the residue is partitioned between EtOAc and

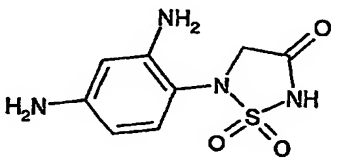
water. The organic layer is dried over anhydrous sodium sulfate (Na_2SO_4) and evaporated. The residue is flash chromatographed on silica gel using 30% → 50% EtOAc in hexanes as eluent to afford the N-sulfamoylated-N-phenylglycine ethyl ester as a yellow solid: API-MS $[M+1]^+ = 259$.

B. 1,1-Dioxo-5-phenyl-1,2,5-thiadiazolidin-3-one sodium salt

A solution of the title A compound, N-sulfamoyl-N-phenylglycine ethyl ester (23 mg, 0.089 mmol) in EtOH is treated with 1N aqueous sodium hydroxide (NaOH, 0.089 mL, 0.089 mmol) and the mixture is stirred at RT for 3 h. The mixture is evaporated to dryness to afford 1,1-dioxo-5-phenyl-1,2,5-thiadiazolidin-3-one sodium salt as a white solid: API-MS $[M-1]^- = 211$.

Example 2

5-(2,4-Diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. Glycine-N-sulfonic acid 2,4-dimethoxybenzylamide

Glycine methyl ester-N-sulfonic acid 2,4-dimethoxybenzylamide (14.9 g, 47.0 mmol), is prepared analogously to the literature procedure as described by Ducry, L.; Reinelt, S.; Seiler, P.; Diederich, F. *Helvetica Chimica. Acta.* **1999**, *82*, 2432-47, and is dissolved in 100 mL of 1,4-dioxane, then 94 mL of 1N aqueous NaOH solution is added. After 120 minutes, the 1,4-dioxane is evaporated in vacuo, and the remaining aqueous solution is extracted with diethyl ether. The aqueous solution is acidified with 1N aqueous HCl solution and extracted with EtOAc two times. The organic layer is dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and evaporated to dryness giving glycine-N-sulfonic acid 2,4-dimethoxybenzylamide: API-MS $[M-1]^- = 303$.

B. 2-(2,4-Dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title A compound, glycine-N-sulfonic acid 2,4-dimethoxybenzylamide (14.3 g, 47.0 mmol) is dissolved in 300 mL of THF, then hydroxybenzotriazole (HOBt, 7.20 g, 47.0 mmol) is added as a solid and stirred until dissolved. EDCI (9.01 g, 47.0 mmol) is added as a solid and stirred for 10 min, followed by the addition of TEA (7.20 mL, 51.7 mmol). The reaction is stirred for 16 h, then evaporated under vacuo. The residue is partitioned

between 1N aqueous HCl solution and EtOAc. The organic layer is dried over anhydrous $MgSO_4$. Filtration followed by evaporation gives an oil which solidified on standing. This is dissolved in hot EtOAc and flash chromatographed on silica gel with 40% EtOAc in hexanes to afford 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: API-MS $[M-1]^-$ = 285.

C. 2-(2,4-Dimethoxybenzyl)-5-(2,4-dinitrophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title B compound, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (303 mg, 1.05 mmol) in dry 1,4-dioxane (5 mL) under nitrogen atmosphere is treated with Cs_2CO_3 (342 mg, 1.05 mmol). 1-Fluoro-2,4-dinitrobenzene (197 mg, 1.05 mmol) is added and the mixture is stirred at RT for 16 h. The solvent is evaporated and the residue is partitioned between EtOAc and 1N aqueous HCl. The organic layer is dried over anhydrous Na_2SO_4 and concentrated. The residue is flash chromatographed on silica gel using 10% → 100% EtOAc in hexanes as the eluent to afford 2-(2,4-dimethoxybenzyl)-5-(2,4-dinitrophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a yellow solid: API-MS $[M-1]^-$ = 451.

D. 2-(2,4-Dimethoxybenzyl)-5-(2,4-diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

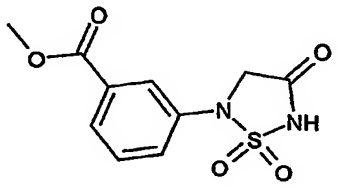
A mixture of the title C compound, 2-(2,4-dimethoxybenzyl)-5-(2,4-dinitrophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (200 mg, 4.42 mmol) in 20 mL of MeOH/EtOAc (3:1) and 10% palladium on carbon (100 mg) is shaken under hydrogen atmosphere at 40 psi for 1 h. The catalyst is removed by filtration and the solvents are evaporated to afford 2-(2,4-dimethoxy-benzyl)-5-(2,4-diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a brown solid: API-MS $[M+1]^+$ = 393.

E. 5-(2,4-Diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of the title D compound, 2-(2,4-dimethoxybenzyl)-5-(2,4-diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (40 mg, 0.10 mmol) is stirred in 4mL of TFA/ CH_2Cl_2 (1:1) at RT for 16 h. The volatiles are evaporated and the residue is stirred in 4 mL of MeCN/water (1:1) for 20 min. The mixture is filtered through a 0.2 μM Acrodisc and the solvents are evaporated. The residue is triturated from diethylether (Et_2O) to give 5-(2,4-diaminophenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one TFA salt as a brown solid: API-MS $[M+1]^+$ = 243.

Example 3

3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)benzoic acid methyl ester



A. 3-[5-(2,4-Dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]benzoic acid methyl ester

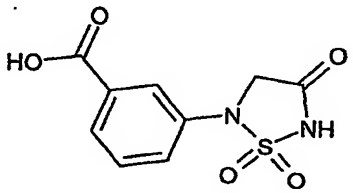
A solution of the title B compound in Example 2, 2-(2,4-dimethoxybenzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (115 mg, 4.02 mmol) and 3-methoxycarbonyl phenylboronic acid (145 mg, 8.04 mmol) in 1,4-dioxane (5 mL) is treated with copper(II) acetate (110 mg, 6.03 mmol) and Cs_2CO_3 (262 mg, 8.04 mmol). The mixture is stirred at RT for 16 h and the solvent is evaporated. The residue is partitioned between EtOAc and 1N aqueous HCl. The organic layer is dried over anhydrous Na_2SO_4 and concentrated. The residue is flash chromatographed on silica gel using 30% EtOAc in hexanes as the eluent to give 3-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]benzoic acid methyl ester as a clear oil: API-MS $[M+NH_4]^+$ = 438.

B. 3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)benzoic acid methyl ester

A solution of the title A compound, 3-[5-(2,4-dimethoxybenzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]benzoic acid methyl ester is stirred in 2 mL of TFA/CH_2Cl_2 (1:1) at RT for 16 h. The volatiles are evaporated and the residue is stirred in 4 mL of MeCN/water (1:1) for 20 min. The mixture is filtered through a 0.2 μM Acrodisc and evaporated. The residue is triturated from Et_2O at –50°C to give 3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)benzoic acid methyl ester as a pink solid: API-MS $[M-1]^-$ = 269.

Example 4

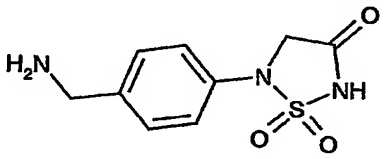
3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid



A solution of sodium hydroxide (105.4 mg, 2.64 mmol) in water (2.54g) is added to a solution of the Example 3 title compound, 3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid methyl ester (37.1mg, 0.137 mmol) in MeOH (5.48 mL). This is allowed to stir 13 h and then is neutralized by addition of 1N aqueous HCl (2.64 mL). The reaction mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in two equal aliquots and eluted at 30 mL/min with a gradient of 100:0 (water containing 0.1% TFA: acetonitrile) for 0 min to 2.5 min, then to 10:90 at 5.5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield 3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid as a white powder: API-Ms $[M-H]^-$ = 255.09.

Example 5

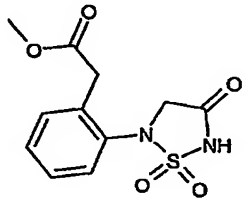
5-(4-Aminomethylphenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



The title compound is prepared analogously to Example 3: API-MS $[M-1]^-$ = 240

Example 6

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester



A. (2-Nitro-phenyl)-acetic acid methyl ester

(2-Nitro-phenyl)-acetic acid (10.93 g, 60.3 mmol) is dissolved in MeOH (200 mL) and HCl gas is bubbled through the solution for 10 min. The reaction is stirred capped for 18 h, then concentrated under reduced pressure to yield (2-nitro-phenyl)-acetic acid methyl ester as a yellow oil.

B. (2-Amino-phenyl) acetic acid methyl ester

The title A compound, (2-nitro-phenyl)-acetic acid methyl ester (5.0 g, 25.6 mmol) is dissolved in MeOH (125 mL) in a Parr Bottle. It is purged with nitrogen, then added PtO_2 (185 mg), then placed on a Parr Shaker under 50 to 55 psi of hydrogen with shaking for 25.5 h. The reaction is opened and filtered through celite, and concentrated to yield (2-amino-phenyl) acetic acid methyl ester as an amber oil: API-MS $[M+1]^+ = 166$.

C. [2-(tert-Butoxycarbonylmethyl-amino)-phenyl]-acetic acid methyl ester

The title B compound, (2-amino-phenyl) acetic acid methyl ester (4.2 g, 25.4 mmol) is dissolved in DMF (30 mL). Powdered potassium carbonate (8.78 g, 63.5 mmol) and tert-butyl bromoacetate (4.12 mL, 27.9 mmol) are added and the reaction is stirred at room temperature for 18 h and then at 50°C for 1 h. The reaction is diluted with water (300 mL) and extracted with EtOAc (2 x 200 mL). Combined EtOAc layers are washed further with water (2 x 100 mL) then brine (100 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give a viscous brown oil. This residue is chromatographed on a 110 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 10:90 (EtOAc:hexane) to 25:75 over 30 min. Fractions containing product are combined and evaporated to yield [2-(tert-butoxycarbonylmethyl-amino)-phenyl]-acetic acid methyl ester as a clear amber oil: API-MS $[M+1]^+ = 280$.

D. N-(tert-Butoxycarbonyl-sulfamoyl)-N-[2-(methoxycarbonylmethyl)-phenyl]-glycine tert-butyl ester

Chlorosulfonylisocyanate (1.42 mL, 16.4 mmol) is added to CH_2Cl_2 (20 mL) in a dry flask under argon balloon, and cooled with stirring in an ice/salt/water bath. tert-Butanol (1.57 mL, 16.4 mmol) is added to this solution and stirred while maintaining the cooling for 1 h. Then a solution of the title C compound, [2-(tert-butoxycarbonylmethyl-amino)-phenyl]-acetic acid methyl ester (3.84 g, 13.7 mmol) and TEA (5.7 mL, 41.1 mmol) in CH_2Cl_2 (90 mL) is rapidly cannulated into this above mentioned stirred, cooled solution. During 18 h the reaction slowly warmed to RT, then concentrated and partitioned between EtOAc and 0.5 N aqueous HCl (2 x 50 mL). The organic solution is washed with brine (25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting residue is chromatographed on a 110 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 10:90 (EtOAc:hexane) to 30:70 over 30 min, maintained at 30:70 for 15 min then to 50:50 over 6 min. Fractions containing product are combined and evaporated to give an oil which on standing in a high vacuum foamed to yield N-(tert-butoxycarbonyl-sulfamoyl)-N-[2-(methoxycarbonylmethyl)-phenyl]-glycine tert-butyl ester as a white foam: API-MS $[M-1]^- = 457$.

E. N-Sulfamoyl-N-[2-(methoxycarbonylmethyl)-phenyl] glycine

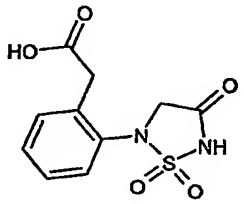
The title D compound, N-(tert-butoxycarbonyl-sulfamoyl)-N-[2-(methoxycarbonyl-methyl)-phenyl]-glycine tert-butyl ester (1.87 g, 4.07 mmol) is dissolved in a mixture of TFA (35 mL) and CH_2Cl_2 (35 mL) and stirred for 30 min. The reaction is concentrated in vacuo, then triturated with diethyl ether to yield N-sulfamoyl-N-[2-(methoxycarbonylmethyl)-phenyl] glycine as a clear glass.

F. [2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester

Carbonyl diimidazole (60 mg, 0.37 mmol) is added as solid to a solution of the title E compound, N-sulfamoyl-N-[2-(methoxycarbonylmethyl)-phenyl] glycine (112 mg, 0.37 mmol) in THF (5 mL). After 65 h, the solvent is removed by evaporation. The residue is taken up in EtOAc and washed with 1N aqueous HCl followed by brine. The organic solution is dried over anhydrous $MgSO_4$, filtered and concentrated. This residue is then evaporated from diethyl ether to yield [2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester as a white foam: API-MS $[M-1]^-$ = 283.

Example 7

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid

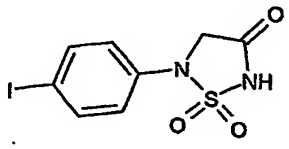


A solution of 2N aqueous NaOH (2.0 mL, 4.0 mmol) is added to a solution of the title F compound in Example 11, [2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester (57 mg, 0.20 mmol) in MeOH (2.0 mL). This is allowed to stir 3 h, then neutralized by addition of 2N aqueous HCl (2.0 mL). The reaction mixture is concentrated on a Savant Speedvac to give a yellow solid (mostly sodium chloride). This is triturated with EtOAc, filtered and evaporated to give a yellow solid. This is dissolved in 2 mL water loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in one aliquot and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant

Speedvac to yield [2-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid as a white solid: API-MS $[M-1]^-$ = 269.

Example 8

5-(4-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one



A. N-(2-Trimethylsilylethoxycarbonyl-sulfamoyl)-N-(4-iodo-phenyl)glycine methyl ester

Chlorosulfonylisocyanate (3.97 mL, 45.6 mmol) is added to CH_2Cl_2 (50 mL) in a dry 300 mL Schlenk flask under argon balloon, and cooled with stirring in an ice/salt/water bath. Trimethylsilylethanol (6.53 mL, 45.6 mmol) is added to this solution and stirred while maintaining the cooling for 1h. Then a solution (4-Iodophenylamino)acetic acid methyl ester (4.43 g, 15.2 mmol, obtained by alkylation of 4-iodoaniline using the method of Tohru Fukuyama et. al., *Tet. Lett.* **1997**, *38* (33), 5831-34) and TEA (8.69 mL, 62.32 mmol) in CH_2Cl_2 (50 mL) is rapidly cannulated into this above mentioned stirred, cooled solution. After 30 min the reaction is poured into 400 mL of 1N aqueous HCl and extracted with EtOAc. The organic layer is washed an additional time with 1N aqueous HCl, separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue is chromatographed on a 110 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 5:95 ($EtOAc:CH_2Cl_2$) to 10:90 over 15 min. Fractions containing product are combined and evaporated to give an oil which on standing in a high vacuum solidified to yield N-(2-trimethylsilylethoxycarbonyl-sulfamoyl)-N-(4-iodo-phenyl)glycine methyl ester as a yellow solid.

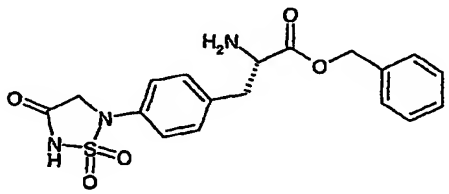
B. 5-(4-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

Tetrabutylammonium fluoride (6.39g, 24.48 mmol) is added as a solid to a solution of the title A compound, N-(2-trimethylsilylethoxycarbonyl-sulfamoyl)-N-(4-iodo-phenyl)glycine methyl ester (3.15 g, 6.12 mmol) in freshly distilled tetrahydrofuran (60 mL). The reaction is stirred under argon balloon and heated in a 90°C oil bath. The reaction is monitored by reverse phase HPLC (YMC CombiScreen Pro C18, 50 x 4.6 mm I.D., particle size S-5 micron, 12 nM) eluting at 3 mL/min with a gradient of 90:10 (water containing 0.1% TFA: acetonitrile) to 10:90 at 7.0 min. Starting material has a retention time of 4.88 min and the product has a retention time of 2.83 min. After 24 h the reaction is poured into 500 mL of

1N aqueous HCl and extracted with EtOAc. The EtOAc is separated and treated with Na_2SO_4 and charcoal. This is filtered through celite and concentrated to give an oil. This is recrystalized with EtOAc/hexane (and some additional charcoal) to yield 5-(4-iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a light yellow powder: mp = 191-193C, API-MS [M-H]$^-$ = 336.8.

Example 9

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid benzyl ester



A. 5-(4-Iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title B compound in Example 8, 5-(4-iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (355.9 mg, 1.05 mmol) is dissolved in tetrahydrofuran (20 mL) in a 40 mL capacity septum capped vial, and stirred under argon balloon. Triphenylphosphine (552 mg, 2.11 mmol) is added as a solid and stirred until dissolved, then 4-methyoxybenzyl alcohol (0.156 mL, 1.26 mmol) is added by syringe. The stirred reaction is cooled in an ice bath, and disopropyl azodicarboxylate (0.415 mL, 2.11 mmol) is added slow dropwise by syringe. After two h, the reaction is concentrated in vacuo, then taken up in CH_2Cl_2 and chromatographed on a 35 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 10:90 (EtOAc:hexane) to 30:70 over 15 min. Fractions containing product are combined and concentrated to give 5-(4-iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid. ^{1}H-NMR (300 MHz, CDCl3) 3.80 (s, 3H), 4.37 (s, 2H), 4.79 (s, 2H), 6.89 (d, J = 7.5, 2H, aryl), 7.03 (d, J = 7.5, 2H aryl), 7.41 (d, J = 7.5, 2H), 7.73 (d, J = 7.5, 2H).

B. (S)-2-tert-Butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester

Zinc foil (99.9% Aldrich 35,602-6, 775 mg, 11.85 mmol) is cut in small pieces and put in a heat dried 40 mL vial with septum cap under argon balloon. Added DMF (freshly distilled from CaH_2 under argon, 4.5 mL) and then 1,2-dibromoethane (0.033 mL, 0.38 mmol), and heated in a 50°C water bath for 10 min. Let cool 5 min, then added trimethylsilyl chloride (0.19 mL, 0.153 mmol) and let stir 25 min. (R)-2-tert-Butoxycarbonylamino-3-iodo-

propionic acid benzyl ester (Fluka, 2.18 g, 5.37 mmol) is then dissolved in DMF (10 mL) and added to the stirred Zinc mixture by syringe. TLC shows this is gone within 15 min (silica gel, 30% EtOAc/hexane, phosphomoybdic acid stain). The title A compound, 5-(4-iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (1.75 g, 3.82 mmol), tri-o-tolylphosphine (232.5mg, 0.764 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (175mg, 0.191 mmol) are then added as solids to a separate heat dried 100 mL Schlenk flask under argon balloon. Rapidly added DMF (13 mL) to this, and then decanted off the zinc reagent formed in the previous vessel from the unreacted zinc, and added it to the Pd catalyst containing mixture. After 1.5 h, the resulting reaction mixture is poured into a mixture of saturated ammonium chloride solution (200 mL) and water (200 mL). Extracted with EtOAc (2 x 250 mL). Washed combined EtOAc layers with water (1 x 200 mL) and brine (1 x 200 mL) and then filtered through celite to removed a strong gray precipitate. Dried over anhydrous Na_2SO_4, filtered and concentrated to give a dark red brown oil. This is chromatographed on a 110 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 0:100 (EtOAc:methylene chloride) to 10:90 over 25 min. Fractions containing product are combined and concentrated to yield (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester as a white solid after tritruration with diethyl ether: API-MS $[M+NH_4]^+$ = 627.0, $[M-HCO_2]^-$ = 654.1.

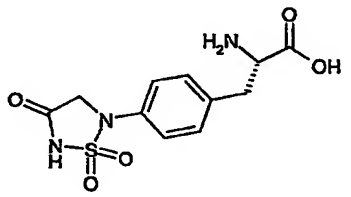
C. (S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid benzyl ester

The title B compound, (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (40 mg, 0.066 mmol) is dissolved in TFA (1.32 mL) containing tert-butyldimethylsilane (0.033 mL, 0.198 mmol) in a 1 dram vial. The reaction is monitored by reverse phase HPLC (YMC CombiScreen Pro C18, 50 x 4.6 mm I.D., particle size S-5 micron, 12 nM) eluting at 3 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) to 10:90 at 7.0 min. Starting material has a retention time of 4.97 min and a new peak has a retention time of 3.09 min, the starting material without the tert-butoxylcarbonyl group as an "intermediate", $[M+H]^+$ = 510. After 25 min at room temperature, the reaction is heated in an 80°C oil bath for an additional 25 min. A new peak by HPLC has a retention time of 2.02 min, corresponding to the desired product. The reaction is removed from the heat, filtered through florisil to remove a black precipitate and concentrated on a Savant Speedvac. The resulting residue is triturated with diethylether to give a white solid. This material is purified on a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D.,

particle size S-5 micron, 12 nM) in two equal aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) at 0 min to 10:90 at 5.0 min, then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield (S)-2-amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid benzyl ester as a white foam: API-MS $[M-1]^-$ = 388.0.

Example 10

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid



A. (S)-2-tert-Butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid

The title B compound in Example 9, (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (107 mg, 0.176 mmol) is dissolved in a 1:1 mixture of EtOAc:EtOH (50 mL) in a 200 mL Parr bottle. 10% Palladium on carbon (30 mg) is added as a solid and the reaction mixture is hydrogenated on a Parr Shaker Apparatus at 41 psi of hydrogen for 2.5 h. The reaction mixture is filtered through celite and concentrated in vacuo to give (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid as a white foam: API-MS $[M-H]^-$ = 518.1.

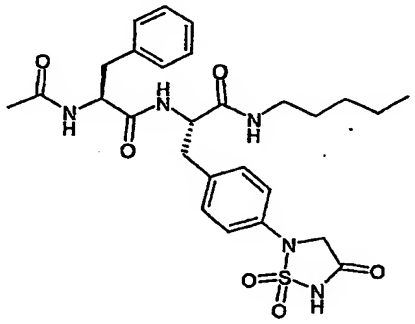
B. (S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid

The title A compound, (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid (84.5 mg, 0.163 mmol) is dissolved in TFA (3.26 mL) containing tert-butyldimethylsilane (0.081 mL, 0.498 mmol) in a 20 vial. The reaction is monitored by reverse phase HPLC (YMC CombiScreen Pro C18, 50 x 4.6 mm I.D., particle size S-5 micron, 12 nM) eluting at 3 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) to 10:90 at 7.0 min. Starting material has a retention time of 3.85 min and a new peak has a retention time of 2.50 min, the starting material without the tert-butoxylcarbonyl group as an "intermediate", $[M+H]^+$ = 420. After 20 min at RT, the reaction is heated in an 80°C oil bath for an additional 45 min. A new peak by HPLC has a retention time of 0.52 min, corresponding to the desired product. The

reaction is removed from the heat, filtered through florisil to remove a black precipitate and concentrated on a Savant Speedvac. The resulting residue is triturated with diethylether to give a white solid. This material is purified on a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in two equal aliquots and eluted at 30 mL/min with a gradient of 100:0 (water containing 0.1% TFA:acetonitrile) at 0 min to 70:30 at 5.0 min, then to 10:90 by 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac then triturated with a mixture of 10% dimethylsulfoxide (DMSO):acetonitrile to yield (S)-2-amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid as a white solid: API-MS $[M-1]^-$ = 298.0.

Example 11

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide



A. ((S)-2-{4-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester

HOBt (27 mg, 0.175 mmol), pentyl amine (0.020 mL, 0.175 mmol) and 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (37 mg, 0.192 mmol) are added to a solution of title A compound in Example 10, (S)-2-tert-Butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid (91 mg, 0.175 mmol) in methylene chloride (4 mL) and this is stirred at RT for 2h. The reaction is then concentrated in vacuo and taken up in EtOAc which is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and then with brine. It is then dried over magnesium sulfate, filtered and concentrated to give a white solid. This is chromatographed on a 10 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 30:70 (EtOAc:hexane) to 60:40 over 10 min. Fractions containing product are combined and evaporated to yield ((S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester as a white solid: API-MS $[M+1]^+$ = 589.

B. (S)-2-Amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide

The title A compond, ((S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester (64 mg, 0.108 mmol) is dissolved in methylene chloride (1 mL), then TFA (1 mL) is added. After 20 min, the solvent is evaporated under stream of nitrogen. The residue is partitioned between EtOAc and saturated sodium bicarbonate, and the organic solution is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide as a white solid: API-MS $[M+1]^+ = 489$.

C. (S)-2-Acetylamino-N-((S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide

HOBt (16 mg, 0.102 mmol), (S)-2-Acetylamino-3-phenyl-propionic acid (21 mg, 0.102 mmol) and EDCI (21 mg, 0.112 mmol) are added to a solution of the title B compound, (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide (50 mg, 0.102 mmol) in methylene chloride (3 mL) and the reaction is stirred at RT for 2.5 h. The reaction is concentrated in vacuo and the product is taken up in EtOAc. The organic solution is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-acetylamino-N-((S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide as a white foam: API-MS $[M+1]^+ = 678$.

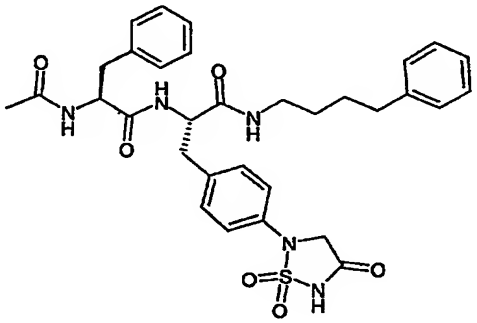
D. (S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide

The title C compound, (S)-2-Acetylamino-N-((S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide (49 mg, 0.07 mmol) is dissolved in TFA (1.4 mL) containing tert-butyldimethylsilane (0.035 mL, 0.21 mmol) and heated at 80°C for 1h. The reaction is concentrated under nitrogen stream to give an oil containing a fine dark suspension. This is taken up in 60% acetonitrile in water, then water (1 mL) is added, and the mixture filtered through a 0.1 micron Acrodisc filter. The resulting mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in three aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) at 0

min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield (S)-2-acetylamino-N-{(S)-1-pentylcarbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide as a white solid: API-MS $[M-1]^-$ = 556.

Example 12

(S)-2-Acetylamino-3-phenyl-N-{(S)-1-(4-phenyl-butylcarbamoyl)-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-propionamide



A. [(S)-2-{4-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester

HOBt (30 mg, 0.196 mmol), 4-phenyl butyl amine (29 mg, 0.196 mmol) and EDCI (41 mg, 0.216 mmol) are added to a solution of the title A compound in Example 10, (S)-2-tert-Butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid (102 mg, 0.196 mmol) in methylene chloride (5 mL) and this is stirred at RT for 2 h. The reaction is then concentrated in vacuo and taken up in EtOAc which is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and brine. The organic solution is then dried over anhydrous $MgSO_4$, filtered and concentrated to give a white solid. This is chromatographed on a 10 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 30:70 (EtOAc:hexane) to 60:40 over 10 min. Fractions containing product are combined and evaporated to yield [(S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester as a white solid: API-MS $[M+1]^+$ = 651.

B. (S)-2-Amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-(4-phenyl-butyl)-propionamide

The title A compound, [(S)-2-{4-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (67 mg, 0.102 mmol) is dissolved in methylene chloride (1 mL), then TFA (1 mL) is added.

After 30 min, the solvent is evaporated under stream of nitrogen. The residue is partitioned between EtOAc and saturated sodium bicarbonate, and the organic solution is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-(4-phenyl-butyl)-propionamide as a gum: API-MS $[M+1]^+$ = 551.

C. (S)-2-Acetylamino-N-[(S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide

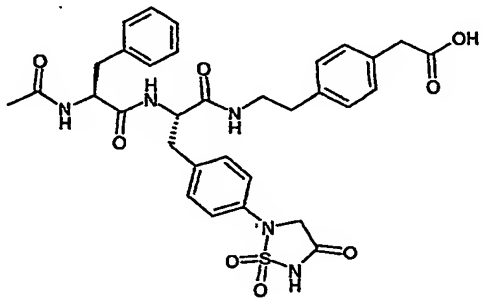
HOBt (16 mg, 0.107 mmol), (S)-2-acetylamino-3-phenyl-propionic acid (22 mg, 0.107 mmol) and EDCI (23 mg, 0.118 mmol) are added to a solution of the title B compound, (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-(4-phenyl-butyl)-propionamide (56 mg, 0.107 mmol) in methylene chloride (3 mL) and the reaction is stirred at room temperature for 4 h. The reaction is then concentrated in vacuo and the product is taken up in EtOAc. The organic solution is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and brine. It is then dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-acetylamino-N-[(S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide as a white foam: API-MS $[M+1]^+$ = 740.

D. (S)-2-Acetylamino-3-phenyl-N-{(S)-1-(4-phenyl-butylcarbamoyl)-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-propionamide

The title C compound, (S)-2-Acetylamino-N-[(S)-2-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide (50 mg, 0.067 mmol) is dissolved in TFA (1.3 mL) containing tert-butyldimethylsilane (0.033 mL, 0.20 mmol) and heated at 80°C for 4 h. The reaction is concentrated under nitrogen stream. The residue is dissolved in diethyl ether and the solvent is evaporated to give a solid. The solid is taken up in acetonitrile / water / DMSO (2:11:1), vortexed, centrifuged and decanted. The resulting solution is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in four aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield (S)-2-acetylamino-3-phenyl-N-{(S)-1-(4-phenyl-butylcarbamoyl)-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-propionamide as an amorphous white foam: API-MS $[M-H]^-$ = 618.

Example 13

[4-(2-{(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionylamino}-ethyl)-phenyl]-acetic



A. (S)-2-Amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester

The title B compound in Example 9, (S)-2-tert-butoxycarbonylamino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (100 mg, 0.164 mmol) is dissolved in a mixture of TFA (3.28 mL) and tert-butyldimethylsilane (0.082 mL, 0.492 mmol) and after 5 min the vial is put on a Savant Speedvac to remove solvets. The residue is triturated with diethyl ether to give a white solid. This is dissolved in CH_2Cl_2 and washed with 5% sodium bicarbonate solution, separated, dried by filtering through anhydrous Na_2SO_4 and evaporated to yield (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester as an oil.

B. (S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester

The title A compound, (S)-2-amino-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (79 mg, 0.155 mmol) and (S)-2-acetylamino-3-phenyl-propionic acid (33.7 mg, 0.162 mmol) are dissolved in CH_2Cl_2 (3.1 mL). HOBt (24.8 mg, 0.162 mmol) is added as a solid, followed by EDCI (31.0 mg, 0.162 mmol) and TEA (0.023 mL, 0.162 mmol) in a slurry of CH_2Cl_2 (1 mL). After 1 h, EtOAc (100 mL) is added and the mixture is washed three times with 2N aqueous HCl (50 mL) followed by saturated sodium bicarbonate (50 mL). The EtOAc layer is dried over anhydrous Na_2SO_4, filtered, concentrated and pumped on high vacuum overnight to yield (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester as a white powder.

C. (S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid

The title B compound, (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (104.3 mg, 0.149 mmol) is dissolved in EtOAc:EtOH (50:50 ; 250 mL) and put in a Parr Shaker bottle along with 10% Palladium on carbon (30 mg). This gas in the bottle is evacuated and replaced with hydrogen at 45 psi and shaken for 1.5 h. The reaction mixture is filtered through celite and concentrated to yield (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid as a light yellow foam.

D. {4-[2-((S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionylamino)-ethyl]-phenyl}-acetic acid tert-butyl ester

The title C compound, (S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid (83.4 mg, 0.137 mmol) is dissolved in DMF (2 mL) and a solution of [4-(2-amino-ethyl) phenyl]-acetic acid tert-butyl ester (32.2 mg, 0.137 mmol) in CH_2Cl_2 (0.5 mL) is added followed by a solution of HOBt (21.9 mg, 0.143 mmol) in DMF:CH_2Cl_2 (50:50, 0.5 mL), and finally EDCI (27.6 mg, 0.143 mmol) and TEA (0.020 mL, 0.143 mmol) as a slurry in CH_2Cl_2 (0.5 mL). The reaction is mixed well to give a homogeneous solution. After 3 h, EtOAc (100 mL) is added and the reaction is washed three times with 2N aqueous HCl (50 mL) followed by saturated sodium bicarbonate (50 mL). EtOAc layer is dried over anhydrous Na_2SO_4, filtered, concentrated and pumped on high vacuum to yield {4-[2-((S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionylamino)-ethyl]-phenyl}-acetic acid tert-butyl ester as an oil.

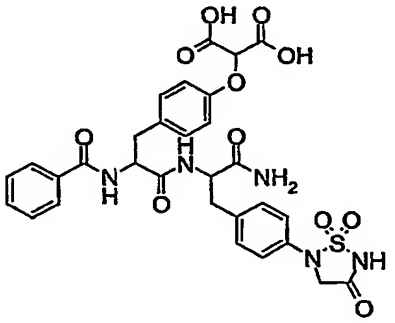
E. [4-(2-{(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionylamino}-ethyl)-phenyl]-acetic

The title D compound, {4-[2-((S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-{4-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionylamino)-ethyl]-phenyl}-acetic acid tert-butyl ester (85.4 mg, 0.103 mmol) is dissolved with a mixture of TFA (2.07 mL) and tert-butyldimethysilane (0.051 mL, 0.309 mmol) and heated in a sealed vial in and oil bath at 80°C for 1 h. The solvent is removed on a Savant Speedvac, and trituration with diethyl ether yielded a white solid after pumping at high vacuum overnight. The resulting solid is dissolved in DMSO:water (1:6, 12 mL) and loaded onto a

preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in five aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to give [4-(2-{(S)-2-((S)-2-acetylamino-3-phenyl-propionylamino)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionylamino}-ethyl)-phenyl]-acetic as a white powder: API-MS $[M-1]^-$ = 648.22.

Example 14

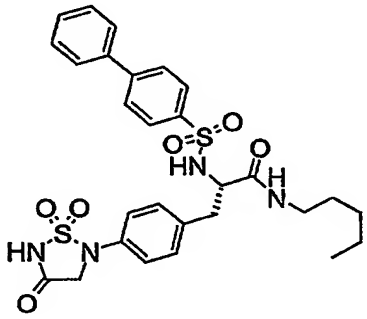
2-[4-(2-Benzoylamino-2-{1-carbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethylcarbamoyl}-ethyl)-phenoxy]-malonic acid



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M+1]^+$ = 668.

Example 15

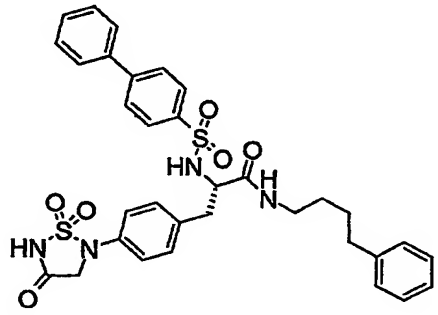
(S)-2-(Biphenyl-4-sulfonylamino)-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 583.

Example 16

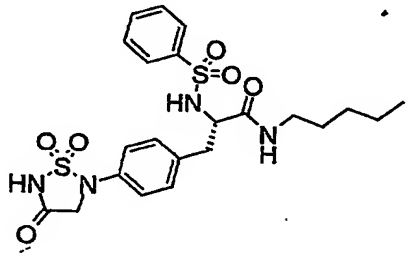
(S)-2-(Biphenyl-4-sulfonylamino)-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 645.

Example 17

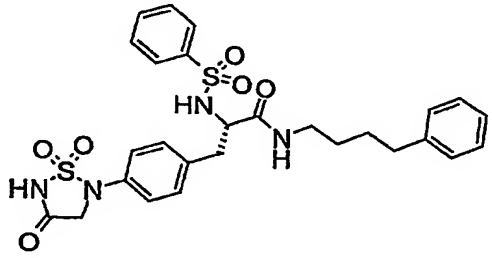
(S)-2-Benzenesulfonylamino-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 507.

Example 18

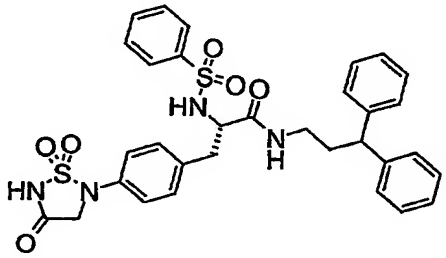
(S)-2-Benzenesulfonylamino-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 569.

Example 19

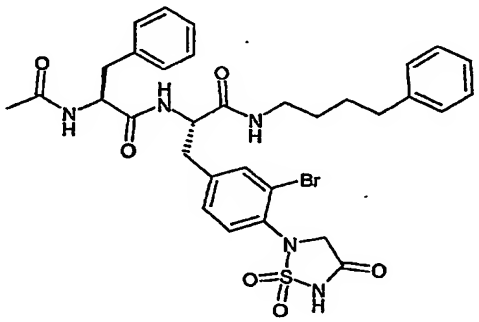
(S)-2-Benzenesulfonylamino-N-(3,3-diphenyl-propyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 631.

Example 20

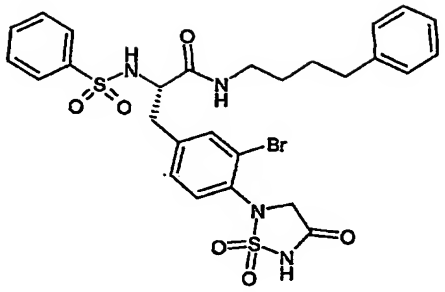
(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M-1]^-$ = 696, 698.

Example 21

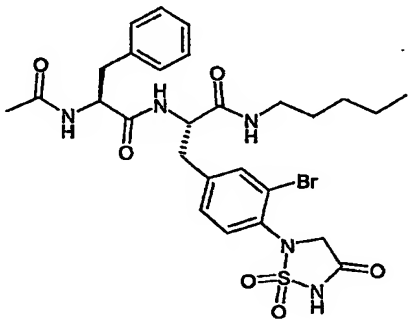
(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M+1]^+$ = 649, 651.

Example 22

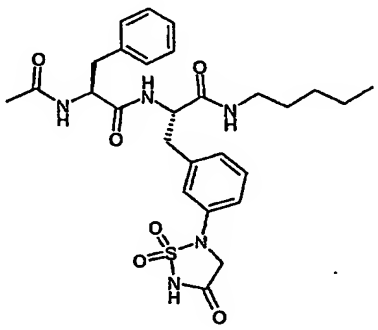
(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide



The title compound is prepared analogously to Examples 12 and 13: API-MS $[M+1]^+$ = 636, 638.

Example 23

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide



A. N-(2-Trimethylsilylethoxycarbonyl-sulfamoyl)-N-(3-iodo-phenyl)glycine methyl ester

Chlorosulfonylisocyanate (3.23 mL, 37.1 mmol) is added to CH_2Cl_2 (100 mL) in a dry 500mL Schlenk flask under argon balloon, and cooled with stirring in an ice/salt/water bath. Trimethylsilylethanol (5.32 mL, 37.1 mmol) is added to this solution and stirred while maintaining the cooling for 1 h. Then a solution (3-Iodo-phenylamino)-acetic acid methyl ester (2.7 g, 9.28 mmol) (obtained by alkylation of 3-iodoaniline using the method of Tohru Fukuyama et. al., Tett. Lett. **38** (33) pp. 5831-34, 1997) and TEA (5.3 mL, 38.04 mmol) in CH_2Cl_2 (50 mL) is rapidly cannulated into this above mentioned stirred, cooled solution. After 2.5 h, the reaction is poured into 400 mL of 1N aqueous HCl and extracted with EtOAc. The EtOAc layer is washed an additional time with 1N aqueous HCl, separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting residue is chromatographed on a 110 g silica gel RediSep (Isco Inc.) column with a 30 mL/min gradient elution of 10:90 (EtOAc:hexane) to 40:60 over 55 min. Fractions containing product are combined and evaporated to give an oil which on trituration with diethyl ether solidified. The solid is collected by filtration to yield N-(2-trimethylsilylethoxycarbonyl-sulfamoyl)-N-(3-iodo-phenyl)glycine methyl ester as a white solid.

B. 5-(3-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

A solution of tetrabutylammonium fluoride (5.88 g, 18.67 mmol) in tetrahydrofuran (40 mL) is added a solution of the title A compound, N-(2-trimethylsilylethoxycarbonyl-sulfamoyl)-N-(3-iodo-phenyl)glycine methyl ester (2.33 g, 4.5 mmol) in tetrahydrofuran (50 mL). The reaction is stirred under argon balloon and heated in a 90°C oil bath. The reaction is monitored by reverse phase HPLC (YMC CombiScreen Pro C18, 50 x 4.6 mm I.D., particle size S-5 micron, 12 nM) eluting at 3 mL/min with a gradient of 90:10 (water containing 0.1% TFA:acetonitrile) to 10:90 at 7.0 min. Starting material has a retention time of 4.82 min and the product has a retention time of 2.81 min. After 24 h, the reaction is poured into 500 mL of 1N aqueous HCl and extracted with EtOAc. The EtOAc is separated and dried with anhydrous $MgSO_4$. This is filtered and concentrated to give 2.047 g of yellow solid. This is triturated with EtOAc/hexane, filtered and evacuated to yield 932mg (61%) product as a white solid: $(M-H)^-$ = 336.9.

C. 5-(3-Iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one

The title B compound, 5-(3-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (932 mg, 2.76 mmol) is dissolved in tetrahydrofuran (20 mL) in a 40 mL capacity septum capped vial, stirred under argon balloon. Triphenylphosphine (1.47 g, 5.51 mmol) is added as a

solid and stirred until dissolved, then 4-methyoxybenzyl alcohol (0.688 mL, 5.51mmol) is added by syringe. The stirred reaction is cooled in an ice bath, and diethyl azodicarboxylate (0.867 mL, 5.51 mmol) is added slow dropwise by syringe. The reaction is stirred 16 h and then recooled and added more diethyl azodicarboxylate (0.433 mL, 2.26 mmol). After 5h, the reaction is concentrated in vacuo, then taken up in CH_2Cl_2 and chromatographed on a 35 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 0:100 (EtOAc:CH_2Cl_2) for 5min, then to 5:95 over 35 min. Fractions containing product are combined, concentrated and recrystalized with EtOAc/hexanes to yield 5-(3-iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) 3.76 (s, 3H, -OMe), 4.79 (s, 2H), 4.88 (s, 2H), 6.92 (d, J=7.5Hz, 2H, aryl), 7.27 (t, J=7.5Hz, 1H aryl), 7.33 (d, J=7.5Hz, 2H aryl), 7.39 (d, J=7.5Hz, 1H aryl), 7.63 (d, J=7.5Hz, 1H aryl), 7.67 (s, 1H aryl).

D. (S)-2-tert-Butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester

Zinc foil (99.9% Aldrich 35,602-6, 118.5 mg, 1.813 mmol) is cut in small pieces and put in a heat dried 1 dram vial with septum cap under argon balloon. DMF (freshly distilled from CaH_2 under argon, 0.4 mL) is added and then 1,2-dibromoethane (0.006 mL, 0.065 mmol), and the mixture is heated in a 50°C water bath for 10 min. The mixture is allowed to cool for 5 min, then trimethylsilyl chloride (0.003 mL, 0.026 mmol) is added and stirring is continued for 25 min. (R)-2-tert-Butoxycarbonylamino-3-iodo-propionic acid benzyl ester (Fluka, 342 mg, 0.844 mmol) is then dissolved in DMF (1 mL) and added to the stirred Zinc mixture by syringe. This is allowed to stir for 1 h. The title C compound, 5-(3-iodo-phenyl)-2-(4-methoxy-benzyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (300 mg, 0.65 mmol), tri-o-tolylphosphine (29.9 mg, 0.13 mmol) and tris(dibenzylideneacetone)-dipalladium(0) (29.9 mg, 0.033 mmol) are added as solids to a separate heat dried 20 mL septum capped vial under argon balloon, and the mixture is diluted with DMF (2 mL). The zinc reagent formed in the previous vessel is then decanted off from the unreacted zinc, and it is added to the Pd catalyst containing mixture. After 1.5 h, the resulting reaction mixture is poured onto water (100 mL), extracted with EtOAc (2 x 100 mL) and the combined EtOAc layers are washed with water (1 x 200 mL) and brine (1 x 200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated to give a yellow oil. This is chromatographed on a 35 g silica gel RediSep column (Isco, Inc.) with a 30 mL/min gradient elution of 0:100 (EtOAc:CH_2Cl_2) to 12:88 over 40 min. Fractions containing product are combined and concentrated to yield (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-

phenyl}-propionic acid benzyl ester as a clear oil: API-MS $[M+NH_4]^+$ = 627.0, $[M-HCO_2]^-$ = 654.1.

E. (S)-2-tert-Butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid

The title D compound, (S)-2-tert-Butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid benzyl ester (187 mg, 0.307 mmol) is dissolved in a 1:1 mixture of EtOAc:EtOH (50mL) in a 200mL Parr bottle. 10% Palladium on carbon (52 mg) is added as a solid and the reaction mixture is hydrogenated on a Parr Shaker Apparatus at 47 psi of hydrogen for 1.33 h. The reaction mixture is filtered through celite and concentrated in vacuo to give (S)-2-tert-butoxycarbonylamino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid as a white foam: API-MS $[M-1]^-$ = 518.1.

F. ((S)-2-{3-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester

HOBt (46.4 mg, 0.302 mmol), pentyl amine (0.035 mL, 0.302 mmol) and EDCI (63.7 mg, 0.332 mmol) are added to a solution of the title E compound, (S)-2-tert-butoxycarbonyl-amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-propionic acid (157 mg, 0.302 mmol) in CH_2Cl_2 (10 mL) and this is stirred at room temperature for 1 h. The reaction is then concentrated in vacuo and the product is taken up in EtOAc. The organic solution is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield ((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester as a white film.

G. (S)-2-Amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide

The title F compound, ((S)-2-{3-[5-(4-Methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-carbamic acid tert-butyl ester (156 mg, 0.265 mmol) is dissolved in CH_2Cl_2 (1 mL), and TFA (1 mL) is added. After 30 min, the solvent is evaporated under stream of nitrogen. The residue is partitioned between EtOAc and saturated sodium bicarbonate. The organic solution is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to yield (S)-2-Amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide as a white solid: API-MS $[M+1]^+$ = 489.

H. (S)-2-Acetylamino-N-((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide

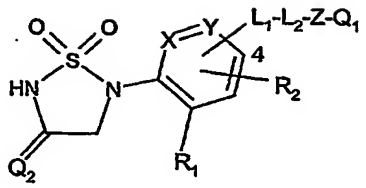
HOBt (40.5 mg, 0.264 mmol), (S)-2-acetylamino-3-phenyl-propionic acid (54.7 mg, 0.264 mmol) and EDCI (50.6 mg, 0.264 mmol) are added to a solution of the title G compound, (S)-2-amino-3-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-N-pentyl-propionamide (129 mg, 0.264 mmol) in CH_2Cl_2 (5 mL) and this is stirred at room temperature for 2 h. The reaction is then concentrated in vacuo and the product is taken up in EtOAc which is successively washed with 1N aqueous HCl, saturated sodium bicarbonate solution and then brine. The organic solution is then dried over magnesium sulfate, filtered and concentrated to yield (S)-2-acetylamino-N-((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide as a white solid: API-MS $[M+1]^+ = 678$.

I. (S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide

The title H compound, (S)-2-acetylamino-N-((S)-2-{3-[5-(4-methoxy-benzyl)-1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl]-phenyl}-1-pentylcarbamoyl-ethyl)-3-phenyl-propionamide (124 mg, 0.183 mmol) is dissolved in TFA (3 mL) containing tert-butyldimethylsilane (0.091 mL, 0.548 mmol) and heated at 80°C for 30 min. Then the reaction is concentrated under nitrogen stream to give an oil containing a fine dark suspension. This is taken up in 60% acetonitrile:water, then water (1 mL) is added, and the mixture filtered through a 0.1 micron Acrodisc filter. The resulting mixture is loaded onto a preparative reverse phase HPLC column (YMC CombiPrep Pro C18, 50 x 20 mm I.D., particle size S-5 micron, 12 nM) in five aliquots and eluted at 30 mL/min with a gradient of 90:10 (water containing 0.1% TFA: acetonitrile) at 0 min to 10:90 at 5 min. Then held at 10:90 until 7 min. Fractions containing product are combined and concentrated on a Savant Speedvac to yield (S)-2-acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide as a white foam: API-MS $[M+1]^+ = 558$.

What is claimed is:

1. A compound of the formula



(I)

wherein

R_1 is hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, nitro, trifluoromethyl, alkynyl, alkylthio, heteroaralkyl, heteroaralkoxy or heteroaryloxy; or

R_1 is optionally substituted alkyl, alkenyl, optionally substituted amino, aralkyl, aralkoxy, aralkylthio, aryloxy, arylthio or cycloalkyl provided that a substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative when Q_2 is oxygen; or

C-R_1 is nitrogen or N→O;

R_2 is hydrogen, halogen, hydroxy, alkoxy, carboxy, cyano, trifluoromethyl, nitro, optionally substituted amino, optionally substituted alkyl, alkylthio, aralkyl, heteroaralkyl, aralkoxy, heteroaralkoxy, aralkylthio, aryloxy, heteroaryloxy, arylthio, or cycloalkyl; or

R_1 and R_2 combined together with the carbon atoms to which R_1 and R_2 are attached form an optionally substituted fused 5- to 6-membered aromatic or heteroaromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one

or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_8 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen, hydroxy, alkoxy, carboxy, optionally substituted alkyl, cycloalkyl, aryl or heteroaryl;

n is zero or an integer from 1 to 4;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl, sulfonyl, acyl or acylamino;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(c) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl

provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond located at the 4-position;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero;

Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2; and

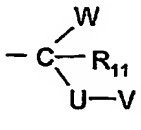
Q_2 is oxygen;

(d) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

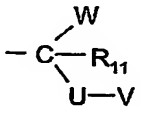
U is $-C(O)-$, $-S(O)_2-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

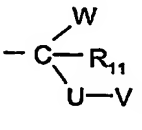
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$, and R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

Q_2 is oxygen, sulfur or NR_{13} wherein

R_{13} is hydrogen, hydroxy or lower alkyl;

X and Y are independently CH or nitrogen; or

-X=Y- is sulfur, oxygen or $-NR_{14}-$ wherein

R_{14} is hydrogen, optionally substituted alkyl, alkoxycarbonyl, acyl, aryloxycarbonyl, heteroaryloxycarbonyl, carbamoyl or sulfonyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

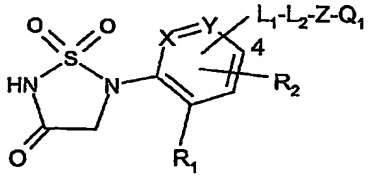
2. A compound according to claim 1 wherein

Q_2 is oxygen;

X and Y are CH; or

-X=Y- is sulfur; or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

3. A compound according to claim 2 of the formula



(IA)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, alkylthio, heteroaralkyl or heteroaralkoxy; or

R_1 is optionally substituted alkyl, aralkyl, aralkoxy or aryloxy provided that a

substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative;

R_2 is hydrogen; or

R_2 is $-C(O)R_3$ wherein

R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

L_1 is a single bond; or

L_1 is carbon which combined together with R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is CH or nitrogen which taken together with R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur; or

L_1 is CH, oxygen, sulfur or nitrogen provided L_2 is carbon which combined together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form an optionally substituted fused 5- or 6-membered aromatic or heteroaromatic ring; or

L_1 is $-CH_2-$, oxygen, sulfur or $-NR_6-$ provided L_2 is CH which taken together with L_1, R_2 and the carbon atoms to which L_1 and R_2 are attached form a fused 5- to 7-membered ring which may be interrupted with one or two heteroatoms selected from oxygen, nitrogen and sulfur wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl; or

L_2 is $-(CHR_7)_n-$ wherein

R_7 is hydrogen;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen or optionally substituted alkyl;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(c) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 and R_2 are hydrogen;

X and Y are CH;

L_1 is a single bond located at the 4-position;

L_2 is $-(CHR_7)_n-$ wherein R_7 is hydrogen and n is zero; and

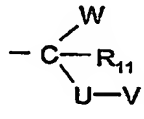
Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2;

(d) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are as defined for R_3;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

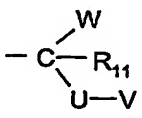
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is $-(CHR_7)_n-$ in which n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is -C(O)R_3 in which R_3 is as defined for R_2;

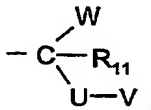
R_{11} is hydrogen, alkyl or aryl;

U is -$(CH_2)_p$- in which p is zero or 1;

V is -$NR_4C(O)R_5$, -$NR_4C(O)OR_5$, -$NR_4C(O)NR_4R_5$ or -$NR_4S(O)_2R_5$ in which R_4 and R_5 are as defined for R_3 provided that

L_2 is -$(CHR_7)_n$- in which n is an integer of 1 or 2; and

Z is -$(CHR_8)_m$- in which m is zero; or

(e) a radical of the formula  wherein

W is -C(O)R_3 in which R_3 is as defined for R_2;

R_{11} is hydrogen, alkyl or aryl;

U is -$(CH_2)_p$- in which p is zero or 1;

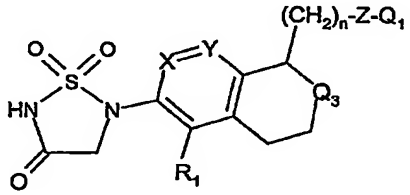
V is -$NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is -NR_4R_5, and R_4 and R_5 are as defined for R_3 provided that

L_2 is -$(CHR_7)_n$- in which n is an integer of 1 or 2; and

Z is -$(CHR_8)_m$- in which m is zero;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

4. A compound according to claim 3 of the formula



(IB)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

n is zero or an integer of 1 or 2;

Z is -$(CHR_8)_m$-, -$(CH_2)_mO(CHR_8)_r$-, -$(CH_2)_mS(CHR_8)_r$- or -$(CH_2)_mNR_9(CHR_8)_r$- wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

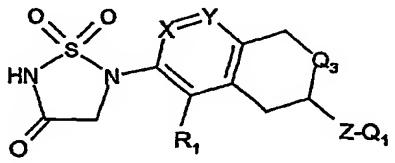
q is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

5. A compound according to claim 3 of the formula



(IC)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl, optionally substituted alkyl, alkylthio, aralkyl, aralkoxy, aryloxy, heteroaralkyl or heteroaralkoxy;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

Q_3 is O, S or $-NR_6-$ wherein

R_6 is hydrogen, optionally substituted alkyl, aralkyl, heteroaralkyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, sulfonyl or acyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

6. A compound according to claim 3 wherein

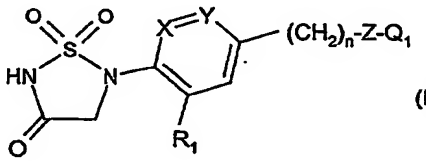
R_2 is hydrogen;

L_1 is a single bond;

L_2 is $-(CH_2)_n-$ in which n is zero or an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

7. A compound according to claim 6 of the formula



(ID)

wherein

R_1 is hydrogen, halogen, alkoxy, trifluoromethyl or alkylthio; or

R_1 is optionally substituted alkyl, aralkyl, aralkoxy or aryloxy provided that a substituent at the 4-position of an aryl group within R_1 is not a methylene or ethylene bridged 2,4-dihydro-1,2,4-triazol-3-one, 2,4-dihydro-1,2,4-triazole-3-thione or 2,4-dihydro-1,2,4-triazol-3-ylidene amine derivative;

n is zero or an integer of 1 or 2;

Z is $-(CHR_8)_m-$, $-(CH_2)_mO(CHR_8)_r-$, $-(CH_2)_mS(CHR_8)_r-$ or $-(CH_2)_mNR_9(CHR_8)_r-$ wherein

R_8 is hydrogen;

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m and r are independently zero or an integer of 1 or 2;

Q_1 is

(a) hydrogen, optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl

provided that Q_1 is not 2-phenyloxazol-4-yl when

R_1 is hydrogen;

X and Y are CH;

L_2 is $-(CH_2)_n-$ wherein n is zero; and

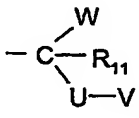
Z is $-(CH_2)_mO(CHR_8)_r-$ wherein R_8 is hydrogen, m is zero and r is 2;

(b) $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

q is an integer of 1 or 2;

(c) a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl; or

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

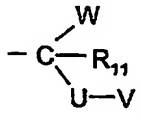
U is $-C(O)-$ or $-(CH_2)_r-$ in which r is as defined for Z;

V is hydroxy, alkoxy, aryl, heteroaryl, optionally substituted alkyl or cycloalkyl; or

V is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

(d) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

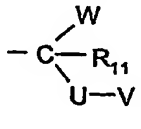
R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero; or

(e) a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is hydroxy or optionally substituted alkoxy; or

R_3 is $-NR_4R_5$ in which R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is $-(CH_2)_p-$ in which p is zero or 1;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl, alkoxy or cycloalkyl; or R_{12} is $-NR_4R_5$ provided that

n is an integer of 1 or 2; and

Z is $-(CHR_8)_m-$ in which m is zero;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

8. A compound according to claim 7 wherein

-X=Y- is sulfur;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

9. A compound according to claim 7 wherein

R_1 is bromide;

X and Y are CH;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

10. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mO(CH_2)_r-$ or $-(CH_2)_mS(CH_2)_r-$ wherein

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

11. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_mNR_9(CH_2)_r-$ wherein

R_9 is hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heteroaryl or acyl;

m is zero;

r is zero or 1;

Q_1 is optionally substituted alkyl, cycloalkyl, aryl or heterocyclyl; or

Q_1 is $-C(O)NR_4R_5$, $-C(O)R_{10}$, $-C(O)OR_{10}$ or $-S(O)_qR_{10}$ wherein

R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{10} is optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

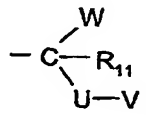
q is an integer of 1 or 2;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

12. A compound according to claim 7 wherein

n is an integer of 1 or 2;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is aryl, heteroaryl, aralkyl or heteroaralkyl;

R_{11} is hydrogen, alkyl or aryl;

U is -C(O)- or $-(CH_2)_r-$ in which r is zero;

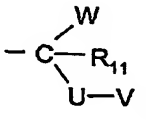
V is aryl, heteroaryl, optionally substituted alkyl or cycloalkyl;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

13. A compound according to claim 7 wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

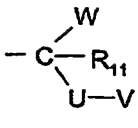
V is $-NR_4C(O)R_5$, $-NR_4C(O)OR_5$, $-NR_4C(O)NR_4R_5$ or $-NR_4S(O)_2R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

14. A compound according to claim 7 wherein

n is 1;

Z is $-(CH_2)_m-$ wherein m is zero;

Q_1 is a radical of the formula  wherein

W is $-C(O)R_3$ in which R_3 is $-NR_4R_5$, and R_4 and R_5 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, heterocyclyl, aralkyl or heteroaralkyl;

R_{11} is hydrogen;

U is $-(CH_2)_p-$ in which p is zero;

V is $-NHC(O)CHR_4NHC(O)R_{12}$ wherein R_{12} is hydrogen, aryl, heterocyclyl, aralkyl, heteroaralkyl, optionally substituted alkyl or alkoxy; or R_{12} is $-NR_4R_5$;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

15. A compound of claim 1 which is selected from a group consisting of:

1,1-Dioxo-5-phenyl-1,2,5-thiadiazolidin-3-one;

5-(2,4-Diamino-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid methyl ester;

3-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-benzoic acid;

5-(4-Aminomethyl-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid methyl ester;

[2-(1,1,4-Trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-acetic acid;

5-(4-Iodo-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one;

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid benzyl ester;

(S)-2-Amino-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionic acid;

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide;

(S)-2-Acetylamino-3-phenyl-N-{(S)-1-(4-phenyl-butylcarbamoyl)-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-propionamide;

[4-(2-{(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionylamino}-ethyl)-phenyl]-acetic acid;

2-[4-(2-Benzoylamino-2-{1-carbamoyl-2-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethylcarbamoyl}-ethyl)-phenoxy]-malonic acid;

(S)-2-(Biphenyl-4-sulfonylamino)-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-(Biphenyl-4-sulfonylamino)-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-pentyl-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-(4-phenyl-butyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Benzenesulfonylamino-N-(3,3-diphenyl-propyl)-3-[4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-propionamide;

(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide;

(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide;

(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide; and

(S)-2-Acetylamino-N-{(S)-1-pentylcarbamoyl-2-[3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-ethyl}-3-phenyl-propionamide;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

16. A compound of claim 1 which is selected from a group consisting of:

(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide;

(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide; and

(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

17. A method for the inhibition of PTP-1B activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

18. A method for the treatment of conditions associated with PTP-1B activity in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

19. The method according to claim 18 wherein the compound is selected from the group consisting of:

(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide;

(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide; and

(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

20. The method according to claim 18, which method comprises administering said compound in combination with a therapeutically effective amount of insulin, insulin derivative or mimetic, insulin secretagogue, insulinotropic sulfonylurea receptor ligand, insulin sensitizer, alpha-glucosidase inhibitor, GLP-1, GLP-1 analog or mimetic, DPP-IV inhibitor, hypolipidemic agent, cholestyramine, fibrate, nicotinic acid, anti-hypertensive agent, anti-obesity agent, or aspirin.

21. A method for modulating glucose levels in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

22. A method for the treatment and/or prevention of diabetes in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

23. The method according to claim 22 wherein the compound is selected from the group consisting of:

(S)-2-Acetylamino-N-[(S)-2-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-1-(4-phenyl-butylcarbamoyl)-ethyl]-3-phenyl-propionamide;

(S)-2-Benzenesulfonylamino-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-(4-phenyl-butyl)-propionamide; and

(S)-2-((S)-2-Acetylamino-3-phenyl-propionylamino)-3-[3-bromo-4-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)-phenyl]-N-pentyl-propionamide;

or a pharmaceutically acceptable salt thereof; or a prodrug derivative thereof.

24. A method for the treatment and/or prevention of metabolic disorders mediated by insulin resistance in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1.

25. A method for the treatment and/or prevention of atherosclerosis in mammals which method comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of claim 1 in combination with a therapeutically effective amount of an HMG-CoA reductase inhibitor.

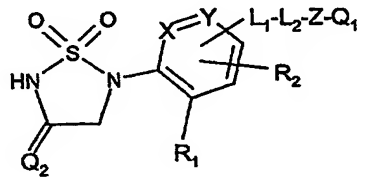
26. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with one or more pharmaceutically acceptable carriers.

27. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a therapeutically effective amount of insulin, insulin derivative or mimetic, insulin secretagogue, insulinotropic sulfonylurea receptor ligand, insulin sensitizer, biguanide, alpha-glucosidase inhibitor, GLP-1, GLP-1 analog or mimetic, DPP-IV inhibitor, hypolipidemic agent, cholestyramine, fibrate, nicotinic acid, anti-hypertensive agent, anti-obesity agent, or aspirin.

CYCLIC SULFAMIDE DERIVATIVES AND METHODS OF USE

ABSTRACT OF THE DISCLOSURE

Compounds of the formula



(I)

provide pharmacological agents which are inhibitors of PTPases, in particular, the compounds of the present invention inhibit PTP-1B, and thus may be employed for the treatment of conditions associated with PTPase activity. The compounds of the present invention may also be employed for inhibition of other enzymes with a phosphotyrosine binding region such as the SH2 domain. Accordingly, the compounds of formula I may be employed for prevention or treatment of insulin resistance associated with obesity, glucose intolerance, diabetes mellitus, hypertension and ischemic diseases of the large and small blood vessels. The compounds of the present invention may also be employed in the treatment, prevention or control of a number of conditions that accompany Type 2 diabetes, including hyperlipidemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, adipose cell tumors and carcinomas such as liposarcoma, dyslipidemia, and other disorders where insulin resistance is indicated. In addition, the compounds of the present invention may be employed to treat or prevent cancer, osteoporosis, neurodegenerative and infectious diseases, and diseases involving inflammation and the immune system.